THE ROLE OF DIABETES, GLYCEMIA, AND GLUCOSE PEAKS IN COGNITIVE IMPAIRMENT AND DEMENTIA AMONG COMMUNITY-DWELLING ADULTS

by
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Abstract

This dissertation explores the association between diabetes, measures of glycemia (average glycemia and glycemic peaks), and cognitive decline and dementia. We also examine the association between diabetes, glycemia, and cognitive impairment in older adults. Additionally, we address two methodological issues: handling missing cognitive data in longitudinal analyses of change in cognitive function, and characterizing the factor structure of the neurocognitive battery used in some of these analyses. We have used data from the Atherosclerosis Risk in Communities (ARIC).

We document that diabetes, higher average glycemic levels (measured by hemoglobin A1c), and more glycemic peaks (measured by 1,5-anhydroglucitol) are associated with accelerated cognitive decline over 20 years. Among persons with diabetes, those with HbA1c ≥7% (poorly controlled diabetes) had greater decline over 20 years than persons with diabetes and HbA1c <7%. Among persons with diabetes, glycemic peaks were associated with incident dementia, independent of HbA1c and other risk factors.

To address attrition, we used multiple imputation by chained equations (MICE) to impute cognitive performance scores. MICE produced unbiased imputations of cognitive function, and simulations showed a substantial reduction in the bias of the 20-year association between diabetes and cognitive decline comparing MICE to analyses without imputed values. Finally, estimated associations between diabetes and 20-year cognitive decline were stronger with MICE than in the analyses without imputed values.

We found that the cognitive battery of 11 tests given at the 2011-2013 ARIC exam represented 3 underlying constructs of memory, language, and sustained attention and processing speed. These constructs were not different by age, race, sex, education, diabetes, and hypertension, providing compelling evidence for the robustness of the cognitive domains measured by the test battery across demographic and vascular factors.

Lastly, we characterized the level of cognitive impairment by diabetes status and glycemia among older adults. Persons with diabetes, longer duration of diabetes, and with glucose peaks had higher estimated prevalence of cognitive impairment.

In conclusion, we have documented the association of diabetes, mean glycemia (HbA1c), and glucose peaks (1,5-AG) with cognitive decline and dementia. This research adds to the literature that diabetes, HbA1c, and glucose peaks are risk factors for cognitive decline and dementia. This has important implications for the prevention of diabetes as a means to prevent or delay cognitive decline. Additionally, the careful management of glycemia among middle-aged adults with diabetes may be an important avenue for prevention of cognitive decline and dementia.

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Abbreviations

1,5-AG	1,5-anhydroglucitiol
ACCORD-MIND	Action to control cardiovascular risk in diabetes – memory in diabetes
AD	Alzheimer's Disease
APOE	Apolipoprotein E
ARIC	Atherosclerosis Risk in Communities
ARIC-NCS	Atherosclerosis Risk in Communities Neurocognitive Study
BIC	Bayesian information criterion
BMI	Body mass index
BNT	Boston naming test
CDR	Clinical dementia rating
CESD	Center for epidemiologic studies depression scale
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CGM	Continuous glucose monitoring
CHD	Coronary heart disease
CI	Confidence interval
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
DSB	Digit span backwards
DSST	Digit symbol substitution test
DWRT	Delayed word recall test
Dx	Diagnosed
HbA1c	Hemoglobin A1c
HDL-c	High-density lipoprotein cholesterol
HR	Hazard ratio
HS	High school
ICD-9	International Classification of Disease, 9th Revision
IPAW	Inverse probability of attrition weighting
LDL-c	Low-density lipoprotein cholesterol
LMT	Logical memory test
MAGE	Mean amplitude of glycemic excursions
MAR	Missing at random
MCAR	Missing completely at random
MICE	Multiple imputation by chained equations
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NACC	National Alzheimer's Disease Coordinating Center
PR	Prevalence ratio
QQ	Quantile-quantile
RMSEA	Root mean square error of approximation
SAPS	Sustained attention and processing speed
SD	Standard deviation
SE	Standard error
SRMR	Standardized root mean residual
TICS-m	Modified telephone interview for cognitive status
TLI	Tucker-Lewis index
TMT	Trail making test
TZD	Thiazolidinedione

WAIS-R	Wechsler adult intelligence scale-revised
WFT	Word fluency test

Introduction

This dissertation examines the association between glycemia and cognitive function and dementia. Specifically, it explores the association between diabetes, prediabetes, average glycemia, and glucose peaks and long-term cognitive decline and dementia. It also describes the prevalence of cognitive impairment in older adults, using a wealth of data to characterize diabetes, glycemia, and cognitive function.

Diabetes and glycemia

Diabetes mellitus is characterized by elevated blood sugar, either because cells are unable to use insulin effectively (insulin resistance) or there is insufficient insulin produced by the pancreas (insulin deficiency)[1]. Type 2 diabetes makes up the vast majority of diabetes in adults, accounting for 90-95% of diagnosed cases[1]. The prevalence of type 2 diabetes has substantially increased in the past few decades, currently affecting over 20 million adults in the U.S[1,2]. The burden accompanying diabetes is considerable, as diabetes is associated with a number of micro- and macrovascular complications, including retinopathy, nephropathy, stroke, and heart disease[3–7].

Glycemia refers to the amount of glucose circulating in the blood. Hyperglycemia occurs when there is an excess amount of glucose circulating, either from insulin resistance, where cells are unable to use insulin as effectively, or from insulin deficiency, where not enough insulin is produce by the pancreas[1]. Fasting glucose and hemoglobin A1c (HbA1c) are the most commonly used biomarkers to characterize hyperglycemia, and are currently used in the diagnosis and management of diabetes[8].

Fasting glucose is a direct measure of glucose, and reflects acute levels of circulating glucose after a period of fasting, usually at least 8 hours. HbA1c is an indirect measure of glucose. It is formed when hemoglobin in the red blood cells is exposed to glucose, and as a result

increases with chronic exposure to elevated plasma glucose levels. HbA1c reflects mean blood glucose over the preceding 2-3 months[9].

Current guidelines from the American Diabetes Association (ADA) categorize an HbA1c of 5.7-6.4% as indicative of an increased risk for diabetes (prediabetes) and an HbA1c ≥6.5% as diagnostic for diabetes[10]. Studies have identified HbA1c values in these ranges as conferring higher burden and risk of retinopathy, kidney disease, stroke, and heart disease[3–7]. Additionally, ADA guidelines suggest a target HbA1c of <7% among persons with diagnosed diabetes, although more flexibility in targets is suggested for older adults given the heterogeneity of clinical and functional status in this population[10].

There is growing interest in the use of alternative biomarkers of hyperglycemia, which measure glycemia over a shorter period (1-3 weeks) compared to HbA1c. 1,5-anhydroglucitol (1,5-AG) is a biomarker that provides information about daily fluctuations in glucose[11,12]. 1,5-AG is a monosaccharide similar to glucose in structure. In the presence of hyperglycemia (levels above the renal filtration threshold of approximately 180 mg/dL), 1,5-AG competes with glucose for renal reabsorption, which causes urine excretion of 1,5-AG to increase and as a result serum levels fall. 1,5-AG reflects hyperglycemic peaks over a short period of time (7-10 days)[11–14]. Studies have documented that in persons with diabetes, 1,5-AG is associated with micro- and macro-vascular disease and death[15,16], independently of average blood glucose (HbA1c). Because of their effect on the vasculature, glucose peaks may be particularly important for cognitive function and dementia, but this association has not been previously studied.

Cognitive impairment and association with diabetes

The U.S. population is rapidly aging, with the number of persons 65 and older expected to reach nearly 70 million by 2030[17]. As the population ages, the health burden of diabetes in older adults will be substantial. Among adults 65 years and older, the prevalence of diabetes and

prediabetes is 22% and 24%, respectively[2]. Additionally, the prevalence of dementia among persons aged 71 and older is 13.9%, and increases with age, with an estimated prevalence of 37.4% among persons 90 years and older[18]. Further, an estimated 22% have cognitive impairment without dementia[19].

A growing body of evidence has found that diabetes affects a wide range of cognitive domains, including motor function, processing speed, memory, and attention, and increases the risk of dementia[20–27]. The mechanisms underlying these associations are unclear, but a number have been proposed, including factors related to the primary metabolic changes associated with diabetes, such as insulin resistance, hypo- and hyper-glycemia, or to its treatment or complications[27–31]. Several studies have shown that the risk of dementia and cognitive decline increases at higher levels of HbA1c[32–34], but few studies have examined associations with glycemic peaks or variability.

Long-term glycemic variability may be related to microvascular and macrovascular complications in persons with diabetes[35], and fluctuating glucose levels have been shown to be more detrimental to neuronal cell functioning in vitro, compared to consistently high or low levels[36]. Glucose peaks are very common among persons with diabetes, even those with HbA1c values <7%[37], and may have deleterious effects on cognitive function.

Gaps in prior evidence

There are several limitations of studies examining the association of diabetes and cognitive decline. The primary limitation of previous studies is short study duration. A review by Cukierman and colleagues[22] published in 2005 included only one study with a mean follow-up of more than 6 years. Subsequently, several studies have reported associations with longer duration: diabetes was associated with a 12-year decline in several tests in the Maastricht Aging Study[38]; a 10-year decline in a global test, memory, and reasoning in 2 Whitehall II studies[32,39]; and an 8-

year decline in 1 of 8 tests in the Framingham Offspring Study[40]. However, only one of these studies reported associations with diabetes diagnosed before age 65 years. Additionally, few studies have reported associations by HbA1c level[41], or used HbA1c in the definition of diabetes. Other limitations include the measurement of diabetes and cognition. Other limitations of current studies include the use of only self-reported diabetes status, lack of use of neuropsychological testing, or not based in a large, community-based sample of adults, potentially limiting generalizability. To our knowledge, no studies have examined the association between glucose peaks and dementia and cognitive decline over 20-years, or examined cognitive function in older adults across the full spectrum of HbA1c. 1,5-AG may be used to identify persons at higher risk of cognitive impairment even within normal values of HbA1c. Finally, a key challenge in studying long-term risk-factor associations in observational studies is that persons at highest risk of complications and cognitive decline are also at highest risk of dropping out the study, potentially biasing results. Few studies have explored the impact of using methods to address this potential bias.

Public health significance

The increasing prevalence of diabetes, along with the aging population, represents a large public health concern, and presents challenges for care of patients with diabetes, especially relating to medication adherence, side-effects (hypo- and hyper-glycemia), and management and prevention of diabetes-related complications; but it also provides the opportunity for intervention and prevention to have substantial impact. There are currently no treatments to stop or reverse cognitive decline or dementia. However, if diabetes is associated with increased risk of cognitive impairment, then preventing or delaying it may have considerable impact on the prevalence and incidence of cognitive impairment and dementia.

Overarching research question and study aims

This dissertation addresses the following overarching research question:

> *What is the association between diabetes, mean glycemia (HbA1c), and glucose peaks (1,5-AG) and cognitive function and dementia?*

To help answer this question, this dissertation addresses the following specific aims:

Aim 1: To characterize the prospective association between diabetes and mean glycemia measured in midlife and 20-year cognitive decline

Aim 2: To develop and validate a model for imputing missing cognitive performance (outcome) data to address bias resulting from study attrition

Aim 3: To characterize the prospective association between glucose peaks (1,5-AG) in midlife and 20-year cognitive decline and incident dementia

Aim 4: To examine the factor structure of ARIC-NCS neuropsychological test battery, and determine if the structure varies by demographic (age, race, sex, education) and vascular factors (hypertension, diabetes)

Aim 5: To estimate the prevalence of cognitive dysfunction among older adults with prediabetes diabetes, and glycemic peaks

Conceptual framework

Figure 1 shows the conceptual framework underlying the aims of this dissertation. We examine two aspects of glycemia, mean glucose and glucose peaks, measured by HbA1c and 1,5-AG, respectively. Cognitive function is measured using neuropsychological testing at three ARIC study visits over 20 years, and dementia is ascertained using community surveillance. Aim 1 examines the association between mean glycemia (HbA1c and diabetes status) and cognitive function over 20 years. Aim 2 examines the utility of multiple imputation to address the issue of

study visit dropout, which may bias estimated associations between diabetes and cognitive function. Aim 3 examines the association between glucose peaks (1,5-AG) and cognitive function over time. Aims 4 and 5 examine cognitive function in older adults. Aim 4 examines the factor structure of the neuropsychological test battery at ARIC-NCS, and identifies the number of underlying cognitive domains and to determine if the structure is similar across demographic and vascular factors. Aim 5 characterizes the prevalence of cognitive dysfunction in three cognitive domains (memory, language, and executive function) by diabetes status, HbA1c, and 1,5-AG. Potential confounders between the association of glycemia and cognition include age, race, sex, education, hypertension, stroke, coronary heart disease, alcohol consumption, cigarette smoking status, and apolipoprotein E.

Organization of this dissertation

This dissertation contains five chapters formatted as publishable papers. The first chapter examines the prospective association between diabetes status (no diabetes, prediabetes, undiagnosed diabetes), glucose control (HbA1c <7% and ≥7%) and cognitive decline over 20-years. This study was published in *Annals of Internal Medicine* in December 2014 (*Ann Intern Med*. 2014;161:785-793. doi:10.7326/M14-0737)[42].

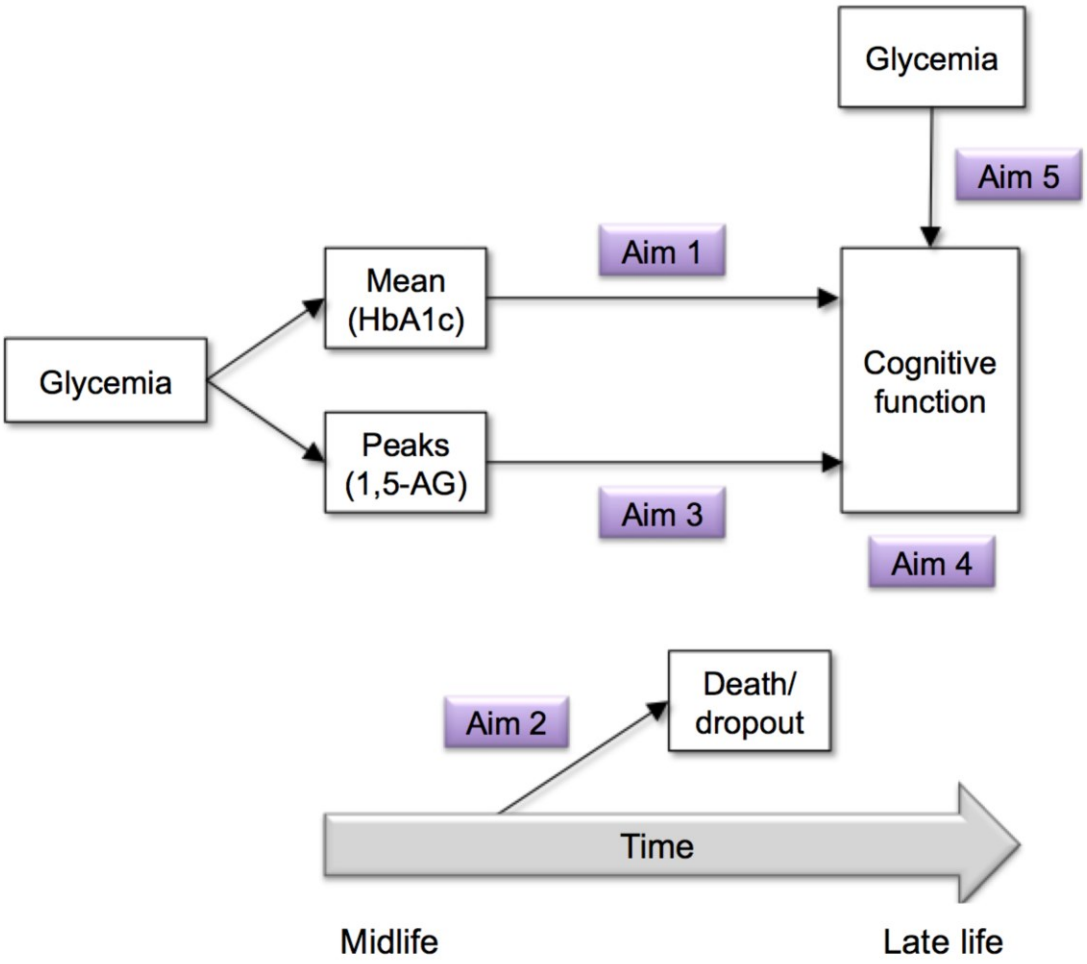
The second chapter explores the use of multiple imputation to account for the impact of differential attrition in long-term prospective studies where auxiliary information exists.

The third chapter is a prospective analysis of the association of glucose peaks (1,5-AG) and cognitive decline and dementia over 20-years.

The fourth chapter examines the factor structure of the ARIC-NCS cognitive battery and examines whether the identified cognitive domains vary by demographic (age, race, sex, education) and vascular factors (diabetes and hypertension). The paper is in press with the journal *Psychological Assessment.*

The fifth chapter examines is a cross-sectional study that characterizes the prevalence of cognitive dysfunction among older adults across clinical categories of HbA1c. It also examines the association of glucose peaks, measured by 1,5-AG, with cognitive dysfunction.

Figure 1. Conceptual framework for the aims of this dissertation



Chapter 1: Diabetes in Midlife and Cognitive Change over 20 Years

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ABSTRACT

Background Type 2 diabetes mellitus is associated with dementia risk, however evidence is limited for possible associations of diabetes and pre-diabetes with cognitive decline.

Objective To determine if diabetes in mid-life is associated with 20-year cognitive decline, and to characterize long-term cognitive decline across clinical categories of hemoglobin A1c (HbA1c).

Design Prospective cohort.

Setting The community-based Atherosclerosis Risk in Communities (ARIC) Study.

Participants 13351 black and white adults aged 48-67 years at baseline (1990-1992).

Measurements Diabetes was defined by self-report of physician diagnosis or medication use or HbA1c≥6.5%. Undiagnosed diabetes, pre-diabetes, and glucose control in persons with diagnosed diabetes were defined using clinical categories of HbA1c. Delayed Word Recall, Digit Symbol Substitution, and Word Fluency tests were used to assess cognitive performance, and were summarized using a global Z-score.

Results Diabetes in midlife was associated with significantly greater cognitive decline over 20 years (adjusted global Z-score difference=-0.15, 95% CI:-0.22,-0.08), representing a 19% greater decline than those without diabetes. Cognitive decline was significantly greater among persons with pre-diabetes (HbA1c 5.7-6.4%) than those without diabetes and HbA1c<5.7%. Participants with poorly controlled diabetes (HbA1c≥7.0%) had a larger decline compared to persons whose diabetes was controlled (adjusted global Z-score difference=-0.16,p-value=0.071). Longer duration of diabetes was also associated with greater late-life cognitive decline (p-value-for-trend=<0.001). No significant differences in the rates of declines were seen in whites compared to blacks (p-value-for-interaction=0.4357).

Limitations Single measurement of HbA1c at baseline, only one test to per cognitive domain, potential geographic confounding of race comparisons.

Conclusions These findings suggest that diabetes prevention and glucose control in midlife may protect against late-life cognitive decline.

INTRODUCTION

The prevalence of diabetes has increased substantially over the past several decades, with a current prevalence of approximately 10%, affecting 21 million adults in the U.S.(1). Type 2 diabetes is an established risk factor for heart disease, stroke, hypertension, blindness, and kidney disease(2-4). The association of diabetes with dementia risk is well established(5-7). The association of diabetes with cognitive decline, however, is less well characterized. Because cognitive decline is a precursor to dementia, strong risk factors for decline can help identify persons who may realize the benefits of early intervention. The effects of diabetes and early hyperglycemic states assessed in mid-life on long-term cognitive decline are relatively uncharacterized(6). Previous studies have been limited by short duration of follow-up, lack of rigorous adjustment for potential confounding variables, and most were limited to whites and conducted in elderly populations, where associations tend to be weaker(8, 9).

Hemoglobin A1c (HbA1c) is a measure of average circulating glucose in the blood over the preceding 2 to 3 months. HbA1c is the standard measure used in the clinical management of diabetes control and is now recommended for the use for diagnosis of diabetes and identification of persons at risk for future diabetes(10). Studies have shown cross-sectional associations between HbA1c and cognitive scores in persons with diabetes(11, 12). However there is little evidence prospectively linking better glycemic control to slower cognitive decline and few studies have examined the association of chronic hyperglycemia below the threshold for a diagnosis of diabetes with long-term cognitive impairment(13-15).

Our objective was to examine the association of diabetes assessed in middle-age with subsequent 20-year cognitive decline in a community-based population of black and white adults. We also examined the associations of hyperglycemia below the threshold for a diagnosis of diabetes (i.e. “pre-diabetes”) and glycemic control in the setting of diabetes with 20-year cognitive decline. An inherent challenge to accurately quantifying the long-term risk factor

associations in observational studies is that participants who are ill are less likely to return for study visits. In this study, we use methods to account for this attrition, which is important in quantifying the long-term associations of diabetes with cognitive decline.

METHODS

Study Population

The Atherosclerosis Risk in Communities Study (ARIC) is a community-based prospective cohort of 15,792 middle aged adults from four U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. The Jackson field center recruited only blacks and Forsyth recruited both blacks and whites. The other two field centers, like Jackson and Forsyth, selected participants by probability sampling; however the racial distribution in these locations at that time resulted in only a small percentage of non-white participants. Participants were seen at four visits approximately three years apart beginning in 1987-1989. A fifth ARIC visit took place in 2011-2013. Cognitive function was evaluated at visits 2 (1990-1992), 4 (1996-1998), and at visit 5 (2011-2013) as part of the ARIC Neurocognitive Study (ARIC-NCS). Detailed information about ARIC can be found elsewhere(16).

Baseline for the present analysis was visit 2, the first visit where cognitive data were collected. Of the 14,348 participants who attended visit 2, we excluded participants who were neither white nor black and the small number of blacks in the Minnesota and Washington county cohorts (n=91), those who were missing one or more cognitive function tests at baseline (n=217), and those missing variables of interest (n=689), giving a final sample size of 13,351 participants at baseline (93% of the visit 2 sample). A flow diagram of the study population and the pattern of visit attendance is included in the Appendix(eFigure1).

Assessment of Cognitive Function

Three cognitive tests were used to assess cognitive function: the Delayed Word Recall Test (DWRT)(17), the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)(18), and the Word Fluency Test (WFT)(19). Protocols for the neuropsychological tests were standardized, and trained examiners administered the tests in a fixed order during one session in a quiet room.

The DWRT is a test of verbal learning and recent memory. Participants were asked to learn 10 common nouns by using each in a sentence. Two exposures to each word were given. After a five-minute filled delay, participants had 60 seconds to recall the words. The score for the DWRT is the number of words recalled.

The DSST is a test of executive function and processing speed. In this 90-second test, participants were asked to translate numbers to symbols using a key. The score is the count of numbers correctly translated to symbols, with a range of possible scores of 0 to 93.

The WFT is a test of executive function and language. Participants were given 60 seconds for each of the letters F, A and S, and were asked to generate as many words as possible beginning with each letter, avoiding proper nouns. The WFT score is the total number of words generated for each of the letters.

To facilitate comparison across cognitive tests, Z scores standardized to visit 2 were calculated for each test by subtracting each participant's test score at each visit from the visit 2 mean and dividing by the visit 2 standard deviation. A composite global cognitive Z score was calculated by averaging the Z scores of the three tests, and was then standardized to visit 2 using the global Z mean and global Z standard deviation from visit 2. Thus, a Z score of -1 would describe cognitive performance that is 1 standard deviation below the mean score at visit 2. Composite global scores derived in this manner have been used in analyses of cognitive change in ARIC(20, 21) and elsewhere(22-24).

Assessment of Diabetes

Diabetes was defined based on self-reported physician diagnosis, diabetes medication use, or HbA1c ≥ 6.5%.

Measurement of Hemoglobin A1c

HbA1c was measured in stored whole blood samples using high-performance liquid chromatography methods standardized to the Diabetes Control and Complications Trial assay (Tosoh A1c 2.2 Plus and Tosoh G7 analyzers, Tosoh, Tokyo, Japan)(25). For analyses of the association between HbA1c category and cognitive decline, HbA1c was categorized using standard clinical cut-points: in persons without a history of diabetes, <5.7%,5.7-6.4%,≥6.5%; and in persons with a history of diabetes, <7.0% and ≥7.0%(10).

Covariates

All covariates used in the regression models were assessed during visit 2 except education, race, and sex, which were assessed during visit 1. The following covariates were evaluated as confounders: age, age-squared, sex, race-field center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks), education (<high school; high school, high school equivalent, or vocational school; college, graduate, or professional school), cigarette smoking (current; former; never), alcohol consumption (current; former; never), body mass index (kg/m^2), hypertension (yes; no – "yes" defined as blood pressure-lowering medication use, systolic blood pressure greater than 140 mmHg, or diastolic blood pressure greater than 90 mmHg), history of coronary heart disease(yes;no – persons who were unsure of their history of heart disease were classified as "no"), history of stroke(yes;no), and apolipoprotein E ε4 genotype(0;1;2 alleles). We also included interaction terms between these variables and time to allow for different rates of decline by these covariates. In sensitivity analyses we treated the following variables as time-varying, updating values at each study visit: cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary

heart disease, and history of stroke. We also additionally adjusted for total cholesterol and lipid-lowering medication use.

Statistical Analysis

We used linear models to estimate associations between diabetes and cognitive decline, fit with generalized estimating equations to account for the within-person correlations of test scores arising from the repeated measures across time; unstructured correlation matrices and robust variance estimates were employed. Time since baseline was modeled using a linear spline with a knot at six years, the mean duration between visits 2 and 4. The spline term allows for a non-linear association between time and cognitive decline, more appropriately fits the study design than would a quadratic term, and was supported by diagnostic lowess smoothers. The primary coefficients of interest were the interactions between diabetes and the time spline terms, which address the hypothesis of greater decline among participants with diabetes adjusting for age and the other covariates. To examine the role of stroke in mediating the association between diabetes and cognitive decline, we censored participant values at the time of stroke, excluding any post-stroke cognitive information from our analyses. To test the robustness of our findings and to mitigate the differences in baseline characteristics between persons with and without diabetes, we reran analyses using propensity score matching. Propensity scores were developed using logistic regression and included sex, age, race-center, education, cigarette smoking, drinking status, hypertension status, prevalent CHD, prevalent stroke, and body mass index. All but 3 participants with diabetes were matched (details in Appendix).

We tested for effect modification between race and diabetes, and tested for linear trend across categories of HbA1c using a variable taking on values 1 through 5 for each category.

In a separate analysis we examined the association of diabetes duration on 14-year cognitive decline, using visit 4 as baseline, and information from all prior visits to categorize diabetes duration. We calculated duration as the difference between the date of the visit 4 exam

and the date of the visit when diabetes was first identified (based on a diagnosis or elevated glucose at any prior visit) and categorized as follows: 1) no diabetes at visit 4 (reference), 2) diabetes duration <3 years, 3) diabetes duration 3-6 years, 4) diabetes duration 6-9 years, or 5) diabetes duration >9 years.

We used an inverse probability of attrition weighting (IPAW)(26, 27) approach to account for potential informative missingness effects (details in Appendix). Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC) and Stata 13.0 (StataCorp LP, College Station TX). PROC GENMOD was used for the generalized linear models, with a repeated statement to account for correlations between observations, and a weight statement to incorporate the IPAW weights.

RESULTS

The mean age of participants at baseline was 57 years, 56% were female, 24% were black, and 13.3% had diabetes (Table 1). Participants with diabetes were older, had less education and lower cognitive scores, and had a more adverse cardiovascular risk factor profile at baseline than those without diabetes. Persons with diabetes at baseline were less likely to attend visit 5 (25% versus 48%), which was largely due to the cumulative incidence of mortality (46% versus 22%) rather than study dropout (29% versus 30%)(Table 1). Those with the lowest Z scores at visit 2 (<5th percentile) were also less likely to attend visit 5, with only 20% returning. Of the 13,351 participants who attended visit 2, 17% did not attend any follow-up visits. Of the remaining 83% of participants who had at least one follow-up visit (10,720 attended visit 4, 5,987 attended visit 5), the median follow-up was 19.3 years (25th,75th percentiles: 6.0, 20.9).

Table 2 shows the estimated 20-year decline from our linear models by diabetes status for global cognitive Z score, DWRT, DSST, and WFT. Diagnosed diabetes was associated with significantly greater decline in global cognitive Z score, the DSST, and the WFT although not in

the DWRT. The average decline over 20 years in global cognitive Z score was 0.78 in persons without diabetes and 0.92 in persons with diabetes (difference: -0.15, 95% CI: (-0.22, -0.08)), i.e. a 19% greater decline among persons with diabetes (-0.15/-0.78=19%). The difference was similar in race-stratified analyses (p-for-interaction=0.4357, Supplemental Tables 1-4). Adjusting for attrition using IPAW strengthened the magnitude of all associations by about 50%. To give these results some context, and because age-related decline in cognitive function is well-established, we used our linear model to estimate how much older a person without diabetes would need to be at baseline to have, on average, a 0.15 lower Z score. We estimated that a participant had to be 4.9 years older. In other words, a 0.15 lower Z score is equivalent to the difference in cognitive performance of a 60 year old versus to a 55 year old, who are otherwise similar (details in Appendix).

Our results were robust to an alternative analytical approach using propensity score matching (Supplemental Table5-6, Supplemental Figure2). Results were also unchanged when we adjusted for total cholesterol, cholesterol-lowering medication use, or when using time-varying covariates. In our stroke mediation analysis, excluding post-stroke cognitive scores reduced the 20-year difference in cognitive decline between persons with and without diabetes by 13%, though results remained significant (Supplemental Table7).

Using visit 4 as baseline shows that duration of diabetes was associated with significantly greater subsequent 14-year cognitive decline (Table 3). The p-value for linear trend across categories was significant for all tests.

Figure 1 shows differences in 20-year decline in global cognitive Z score by clinical categories of HbA1c. The p-value for linear trend across all categories was significant (p=0.0367 without adjustment for attrition and p=0.006 for the attrition-adjusted values). Persons without diagnosed diabetes but HbA1c of 5.7-6.4% at baseline had significantly more cognitive decline over 20 years (adjusted difference in global cognitive Z score=-0.07, p-value=0.005) compared to

persons without diabetes and HbA1c<5.7%. Persons without diagnosed diabetes but with HbA1c≥6.5% (undiagnosed diabetes) also had a greater decline in cognitive score compared to the reference group, however this difference was not statistically significant (p-value=0.105). The greatest decline was found in the group with diabetes and HbA1c≥7.0%. Participants in this group had a larger decline compared to persons with diabetes and HbA1c<7% (adjusted difference in global cognitive Z score=-0.16, p-value=0.071), which was borderline statistically significant. Adjusting for attrition strengthened the magnitude of all associations.

DISCUSSION

In this community-based population, we found significantly greater cognitive decline among both black and white adults with diabetes compared to those without diabetes at baseline, with 20-year cognitive decline 19% larger in this group for the global score, or 30% larger after accounting for attrition. Duration of diabetes appeared to be a factor, with later life 14-year decline greater for participants with longer duration of diabetes. There were trends of increased cognitive decline across clinical categories of HbA1c, even among persons without a history of diabetes. Those with HbA1c in the 5.7-6.4% range (pre-diabetes) and those with HbA1c≥6.5% (undiagnosed diabetes) at baseline had larger declines over 20 years than those with HbA1c<5.7%. Excluding person with stroke post-baseline attenuated the results slightly, suggesting stroke partially mediates the association between diabetes and cognitive decline.

The observed association of diabetes with decline in global cognitive function was primarily driven by declines in the DSST and WFT, which reflect impairments in the processing speed and executive function domains(28, 29). These results suggest that the association of diabetes with cognitive function may involve the subcortical microvasculature that damages white matter pathways or subcortical grey matter in other ways(30-32). However, we also found

associations with memory, but only in whites, after adjustment for attrition. This may be due to the fact that the DWRT, with only 10 words, is insensitive to small declines in memory.

Previous studies of diabetes and cognitive decline have mostly been short in duration: Cukierman's review included only one study with mean follow-up of more than 6 years' duration(6). In four recent reports, diabetes was associated with 12-year decline in several tests in the Maastricht Study(33), 10-year decline in a global test, memory, and reasoning in two Whitehall II studies(15, 34), and 8-year decline in one of 8 tests in the Framingham Offspring Study(35). However, only one of these reported associations with diabetes diagnosed before age 65.

ACCORD-MIND, a randomized clinical trial, showed that tight glucose control in elderly diabetics with high cardiovascular risk did not reduce cognitive decline measured by DSST(13, 14). Some have postulated that the lack of benefit in ACCORD-MIND may have been due to the older age of participants (mean age 63), the short treatment period (3.3 years), and a higher frequency of hypoglycemic episodes in the treatment compared to the control arm. However, our observations that higher HbA1c levels were associated with greater 20-year cognitive decline even in persons without a diagnosis of diabetes, and that longer duration of diabetes was associated with greater cognitive decline, suggests that a long-term trial, if one were feasible, could demonstrate the cognitive benefit of glycemic control. The potential benefit of early intervention deserves further study(36).

Some limitations of our study deserve consideration. We had only one test in each cognitive domain at each visit and only a single measurement of HbA1c at baseline. Blacks in ARIC come from just 2 study sites, limiting our ability to fully separate the effects of race from those of geography. Attrition is a likely concern for any long-term study. However, our attrition-adjustment likely provides less biased estimates of the effect of diabetes on cognition than when attrition is ignored, as in most prior reports. Although we adjusted for attrition using a broad set

of available data, it is possible that our method of adjustment does not fully account for the effects of drop out, especially dropout directly related to low cognitive function, and our estimate of the association of diabetes with cognitive decline may remain conservative. As this is an observational study, we cannot conclude that the link between diabetes and cognitive decline is causal, and we cannot rule out the possibility of residual confounding.

Strengths of this study include the large community-based population of blacks and whites, rigorous assessment of variables that might affect the association between diabetes and cognitive function, and our methods to reduce the effects of dropout. The evaluation of cognitive change over time, with 20-year duration of follow-up with cognitive function assessed at several time points, is also a particular strength of this study. Rather than assessing dementia or cognitive performance at a single time point, examining scores over time reduces the influence of confounding variables(20).

Maintaining cognitive function is a critical aspect of successful aging and for ensuring a high quality of life. Diabetes and glucose control are potentially modifiable and may offer an important opportunity for the prevention of cognitive decline, thus delaying progression to dementia. At the population level, delaying the onset of dementia by even a couple of years could reduce the prevalence of dementia by more than 20% over the next 30 years(37).

This study documents that diabetes and pre-diabetes in middle age are associated with greater cognitive decline over the subsequent two decades. The association with cognitive decline was stronger for diabetes of longer duration, and our findings were similar in black and white adults. These data suggest that primary prevention of diabetes or glucose control in midlife may protect against later-life cognitive decline.

Table 1. ARIC population visit 2 baseline characteristics by diabetes status

	Total (N=13,351)	Diabetes (N=1,779)	No Diabetes (N=11,572)
Age	57.0 (5.7)	58.2 (5.7)	56.8 (5.7)
Female, %	55.6	57.2	55.3
Visit 5 Attendance, %			
Died before visit 5	25.4	46.4	22.1
Alive, but did not attend	29.8	28.6	30.0
Attended	44.8	25.1	47.9
Race-Center, %			
Minneapolis - White	26.9	13.9	28.8
Washington County - White	26.2	24.6	26.4
Forsyth - White	23.3	16.5	24.4
Forsyth - Black	2.7	4.9	2.4
Jackson - Black	21.0	40.1	18.0
Cognitive scores			
Global cognitive Z score	0.00 (1.0)	-0.52 (1.0)	0.08 (1.0)
Delayed word recall test, number of words Recalled	6.6 (1.5)	6.1 (1.6)	6.7 (1.5)
Digit symbol substitution test, number of symbols translated	44.7 (14.2)	36.9 (14.4)	45.9 (13.7)
Word fluency test, number of words generated	33.2 (12.5)	29.3 (12.4)	33.8 (12.4)
Hemoglobin A1c	5.8 (1.2)	8.0 (2.1)	5.4 (0.4)
Prevalent coronary heart disease, %	5.7	11.1	4.8
Prevalent stroke, %	1.7	4.4	1.3
Apolipoprotein E ε4 alleles, %			
0	69.2	69.4	69.2
1	28.1	27.8	28.2
2	2.6	2.9	2.6
Hypertension, %	35.6	59.0	32.0
Body mass index, kg/m^2	28.0 (5.4)	31.4 (6.1)	27.4 (5.1)
Total cholesterol level			
mg/dL	210 (39.5)	216 (45.5)	209 (38.4)
mmol/L	5.43 (1.02)	5.57 (1.18)	5.41 (0.99)
HDL cholesterol level			
mg/dL	49.4 (16.7)	43.1 (14.2)	50.4 (16.8)
mmol/L	1.28 (0.43)	1.11 (0.37)	1.30 (0.44)
Triglyceride level			
mg/dL	136 (90.3)	178 (135.3)	130 (79.4)
mmol/L	1.54 (1.02)	2.01 (1.53)	1.46 (0.90)
Education, %			
Less than high school	21.2	34.9	19.1
High school, graduate equivalence degree, or vocational school	41.8	37.9	42.3
College, graduate, or professional school	37.0	27.2	38.6
Cigarette smoking status, %			
Current	22.3	20.8	22.5
Former	37.9	37.0	38.1
Never	39.8	42.2	39.4
Alcohol consumption, %			
Current	56.6	36.0	59.7

	Former	20.8	33.2	18.9
	Never	22.6	30.8	21.3

Age, cognitive scores, hemoglobin A1c, body mass index, total cholesterol, HDL cholesterol, and triglycerides are means (SD). All other values are percentages.

Table 2. Average difference in 20-year decline in global cognitive Z score, delayed word recall, digit symbol substitution, and word fluency among persons with a history of diagnosed diabetes compared to persons without diabetes

No attrition adjustment

Test	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference* Estimate (95% CI)	Percent†
Global Z	**-0.78 (-0.80, -0.75)**	**-0.92 (-1.00, -0.85)**	**-0.15 (-0.22, -0.08)**	19%
Delayed Word Recall Test	**-0.98 (-1.02, -0.94)**	**-1.04 (-1.15, -0.92)**	-0.06 (-0.17, 0.06)	6%
Digit Symbol Substitution Test	**-0.69 (-0.71, -0.67)**	**-0.82 (-0.87, -0.77)**	**-0.13 (-0.18, -0.08)**	19%
Word Fluency Test	**-0.17 (-0.19, -0.14)**	**-0.28 (-0.35, -0.22)**	**-0.12 (-0.18, -0.06)**	71%

Attrition-adjusted

Test	20 year decline – No diabetes	20 year decline – Diabetes	Difference*	Percent†
Global Z	**-0.79 (-0.82, -0.76)**	**-1.01 (-1.11, -0.92)**	**-0.23 (-0.32, -0.13)**	29%
Delayed Word Recall Test	**-1.01 (-1.05, -0.96)**	**-1.09 (-1.22, -0.96)**	-0.09 (-0.22, 0.04)	9%
Digit Symbol Substitution Test	**-0.70 (-0.72, -0.68)**	**-0.87 (-0.94, -0.81)**	**-0.18 (-0.24, -0.11)**	26%
Word Fluency Test	**-0.17 (-0.20, -0.14)**	**-0.37 (-0.47, -0.28)**	**-0.21 (-0.31, -0.10)**	124%

* Calculated as the difference in 20-year decline between persons without and with diabetes (negative values indicate greater decline in persons with diabetes)

† Calculated as the difference expressed as a percentage of the decline in those without diabetes. That is, (decline in participants without diabetes – decline in participants with diabetes)/(decline in participants without diabetes); thus a value of 19% indicates a 19% greater decline in those with diagnosed diabetes compared to those without. Note that the differences and percent declines are calculated before rounding of 20-year estimates.

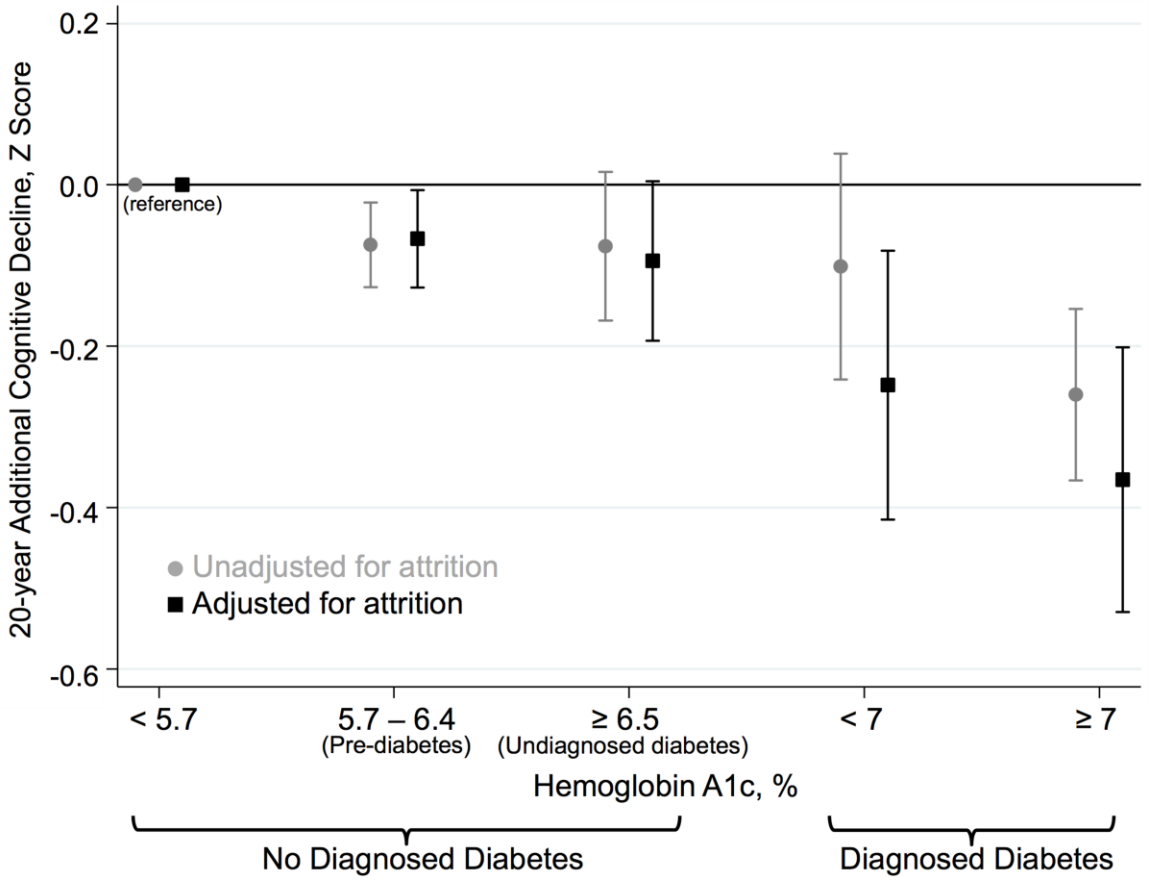
Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=30,058 total records, with N=13,351 participants at visit 2(N=1,779 with diabetes), N=10,720 at visit 4(N=1,209 with diabetes), and N=5,987 at visit 5(N=446 with diabetes).

Table 3. Average difference in 14-year decline in global cognitive Z score, delayed word recall test, digit symbol substitution test, and word fluency test comparing persons of varying diabetes duration to persons without diabetes

		No attrition adjustment		Attrition adjusted	
Test	Diabetes duration (years)	Absolute 14-year decline Estimate (95% CI)	Difference* Estimate (95% CI)	Absolute 14-year decline Estimate (95% CI)	Difference* Estimate (95% CI)
Global Z	No diabetes	**-0.67 (-0.70, -0.64)**	(reference)	**-0.68 (-0.71, -0.65)**	(reference)
	< 3	**-0.81 (-0.90, -0.71)**	**-0.13 (-0.23, -0.04)**	**-0.85 (-0.97, -0.73)**	**-0.18 (-0.30, -0.05)**
	3 - 6	**-0.72 (-0.82, -0.62)**	-0.05 (-0.14, 0.05)	**-0.73 (-0.83, -0.63)**	-0.05 (-0.15, 0.05)
	6 - 9	**-0.81 (-0.93, -0.68)**	**-0.13 (-0.26, -0.01)**	**-0.86 (-1.01, -0.72)**	**-0.19 (-0.34, -0.04)**
	> 9	**-0.85 (-0.95, -0.74)**	**-0.18 (-0.28, -0.07)**	**-0.91 (-1.02, -0.79)**	**-0.23 (-0.34, -0.12)**
	p-value-for-trend	**0.001**	-	**0.002**	-
Delayed Word Recall Test	No diabetes	**-0.89 (-0.94, -0.85)**	(reference)	**-0.90 (-0.95, -0.85)**	(reference)
	< 3	**-0.98 (-1.11, -0.84)**	-0.08 (-0.22, 0.06)	**-1.02 (-1.19, -0.86)**	-0.12 (-0.29, 0.05)
	3 - 6	**-0.96 (-1.10, -0.81)**	-0.06 (-0.21, 0.08)	**-0.97 (-1.13, -0.82)**	-0.07 (-0.23, 0.08)
	6 - 9	**-0.99 (-1.18, -0.81)**	-0.10 (-0.28, 0.09)	**-1.01 (-1.20, -0.82)**	-0.11 (-0.30, 0.08)
	> 9	**-1.05 (-1.20, -0.89)**	-0.16 (-0.31, 0.00)	**-1.09 (-1.26, -0.91)**	**-0.19 (-0.36, -0.02)**
	p-value-for-trend	**0.003**	-	**0.003**	-
Digit Symbol Substitution Test	No diabetes	**-0.56 (-0.58, -0.53)**	(reference)	**-0.56 (-0.58, -0.54)**	(reference)
	< 3	**-0.68 (-0.75, -0.61)**	**-0.12 (-0.19, -0.05)**	**-0.70 (-0.78, -0.62)**	**-0.14 (-0.22, -0.06)**
	3 - 6	**-0.62 (-0.69, -0.55)**	-0.07 (-0.14, 0.00)	**-0.62 (-0.68, -0.55)**	-0.05 (-0.12, 0.01)
	6 - 9	**-0.65 (-0.74, -0.55)**	-0.09 (-0.18, 0.00)	**-0.68 (-0.77, -0.58)**	**-0.11 (-0.21, -0.02)**
	> 9	**-0.73 (-0.81, -0.64)**	**-0.17 (-0.25, -0.09)**	**-0.77 (-0.87, -0.67)**	**-0.21 (-0.31, -0.11)**
	p-value-for-trend	**<0.001**	-	**<0.001**	-
Word Fluency Test	No diabetes	**-0.13 (-0.16, -0.11)**	(reference)	**-0.13 (-0.16, -0.10)**	(reference)
	< 3	**-0.20 (-0.29, -0.12)**	-0.07 (-0.16, 0.01)	**-0.23 (-0.33, -0.13)**	**-0.10 (-0.20, -0.00)**
	3 - 6	**-0.14 (-0.23, -0.05)**	-0.01 (-0.10, 0.09)	**-0.13 (-0.23, -0.03)**	0.00 (-0.10, 0.11)
	6 - 9	**-0.27 (-0.39, -0.16)**	**-0.14 (-0.25, -0.03)**	**-0.36 (-0.53, -0.18)**	**-0.22 (-0.41, -0.04)**
	> 9	**-0.24 (-0.33, -0.15)**	**-0.11 (-0.20, -0.02)**	**-0.29 (-0.39, -0.18)**	**-0.15 (-0.26, -0.05)**
	p-value-for-trend	**<0.001**	-	**0.001**	-

* Calculated as the difference in 14-year decline between persons with no diabetes at either visit and persons who have prevalent diabetes at visit 2 or develop diabetes between visits 2 and 4 (negative values indicate greater decline in those with prevalent or incident diabetes)
Note: bold values indicate p-value < 0.05. Baseline for this analysis was visit 4, and visits 1,2, and 3 were used to calculate diabetes duration. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=16,707 total records, with N=10,720 at visit 4(N=1,209 with diabetes) and N=5,987 at visit 5(N=446 with diabetes).

Figure 1. Difference in global cognitive Z score decline by clinical categories of hemoglobin A1c compared to decline in persons without diabetes with hemoglobin A1c < 5.7%.



Legend: Adjusted for attrition refers to the inverse probability of attrition weighting used to account for participant death or dropout during follow-up. Estimates (95% confidence intervals) are from generalized linear models fit using generalized estimating equations for global cognitive Z score, with adjustment for age, age-squared, race-center, sex, education, cigarette smoking status, drinking status, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, body mass index, interactions between these variables and time (except for drinking status and history of coronary heart disease, which were not significant), and interactions between race-center and sex, hypertension, and education. Hemoglobin A1c was categorized using the standard clinical cut-points based on American Diabetes Association criteria (in participants without a diagnosis of diabetes (N=12,107): <5.7% (N=9,031), 5.7-6.4% (N=2,365), and ≥6.5% (N=711); in participants with diagnosed diabetes(N=1,244): <7% (N=415), ≥7% (N=829).

Chapter 2: Multiple Imputation of Cognitive Performance as an Outcome

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ABSTRACT

BACKGROUND: Longitudinal studies of cognitive performance are sensitive to dropout, as participants experiencing cognitive deficits are less likely to attend study visits. This may bias estimated associations between exposures of interest and cognitive decline, especially if exposures also predict dropout. Multiple imputation is a powerful tool for handling missing data, however its use for missing cognitive outcome measures remains limited.

METHODS: We use multiple imputation by chained equations (MICE) to impute cognitive performance scores of participants who did not attend the 2011-2013 follow-up exam of the Atherosclerosis Risk in Communities Study, using data available for subsets of participants. We examined the validity of imputed scores by setting to missing cognitive scores of a subset of participants and comparing observed and imputed values, and by using data simulated under varying assumptions. Finally, we examined differences in the estimated association between diabetes at baseline and 20-year cognitive decline with and without imputed values.

RESULTS: Validation using observed data showed MICE produced unbiased imputations in living and deceased participants. Simulations showed a substantial reduction in the bias of the 20-year association between diabetes and cognitive decline comparing MICE (3% bias) to analysis of available data only (23% bias) in a construct where missingness was strongly informative but realistic. Associations between diabetes and 20-year cognitive decline were substantially stronger with MICE than in the analyses without imputed values.

CONCLUSIONS: Our study suggests when informative data are available for non-examined participants, MICE can be an effective tool for imputing cognitive performance and improving the characterization of long-term cognitive decline.

INTRODUCTION

Missing data is a common problem in epidemiologic studies. In longitudinal studies, the focus is often on how a baseline exposure is associated with changes in an outcome. Here, since participants who do not attend subsequent study visits are likely informatively different from those who do attend, associations may be biased if missing data are not handled appropriately.

Multiple imputation is a powerful tool for dealing with missing data[1–4]. However, use of imputation for outcome measures of cognitive decline remains limited[5,6], perhaps because other methods are effective for correcting potential biases. For example, maximum likelihood methods, routinely used in fitting mixed models, account for bias due to missing data when missingness is random with respect to variables included in primary analyses[7]. Inverse probability of attrition weighting methods and shared parameter models[8–11] are also used to account for biases associated with dropout and death (under specific assumptions), and allow use of additional variables not included in primary analyses.

Multiple imputation is particularly useful when data are available for at least a subset of participants who did not attend all study visits. Large epidemiologic studies with repeat examinations often collect such data through morbidity and mortality surveillance or follow-up telephone calls. When such data are also collected for individuals who attend study visits, multiple imputation may effectively address potential biases, especially compared to other analytical methods.

Participants with low cognitive performance are typically less likely to attend follow-up examinations[12–15]. Data collected via surveillance of hospitalizations and telephone calls may identify participants believed to have dementia or mild cognitive impairment, and such identification is indicative of the low cognitive test scores that would be found had they been examined. Since a full cognitive battery is often not available for such participants, methods to translate such information into a cognitive battery score are needed.

In this study we imputed cognitive performance scores of participants from the Atherosclerosis Risk in Communities (ARIC) Study, who did not attend the 2011-2013 exam, using multiple imputation by chained equations[2,16]. We present validation results using both observed and simulated data to test the robustness of the imputation under different assumptions. To illustrate the utility of multiple imputation to address issues of dropout, we examined the association of diabetes at baseline as the exposure of interest (which is also a risk-factor for study dropout and death) with cognitive performance over 20-years (the outcome).

METHODS

Study population

The ARIC study is a community-based, prospective cohort of 15,792 middle-aged adults from four communities in Maryland, Minnesota, Mississippi, and North Carolina[17]. Participants were examined at four triennial visits, beginning in 1987-1989. A fifth examination occurred in 2011-2013. Participants in North Carolina and Mississippi also had cognitive assessment at ancillary visits in a subsample of participants who participated in the Brain MRI or Carotid MRI (2004-2005) studies (N=2790). Baseline for the present study was visit 2 in 1990-1992 (where cognitive assessment began), so we excluded participants who did not attend baseline (N=1444) or who were neither black nor white(N=91). Institutional review boards from all study sites approved the study, and all participants provided informed consent.

Diabetes assessment

Diabetes at baseline (1990-1992) was defined as self-reported physician diagnosis, diabetes medication use, or a hemoglobin A1c level ≥6.5%.

Cognitive assessment at study visits

Cognitive function was assessed at visits 2, 4, and 5 using 3 tests: Delayed Word Recall[18], Digit Symbol Substitution[19], and Word Fluency[20]. We standardized each test score to baseline by subtracting the test mean (at baseline) from each participant's score and

dividing by the test standard deviation (SD, at baseline). A global Z score, calculated by averaging the Z score of the three tests, was likewise standardized to baseline. The global Z score was the outcome of interest and the focus of the imputation.

Auxiliary measures of cognitive function

Information about cognitive function for participants who did not attend visit 5 was available through the modified Telephone Interview for Cognitive Status (TICS-m) questionnaire, suspect dementia status, and the Clinical Dementia Rating (CDR) scale.

The TICS-m, a test of cognitive function given over the telephone[21–23], was offered to all participants who did not attend visit 5 (completed for N=1327), and to a random subsample of participants who attended visit 5 (N=255).

Participants were classified as having suspect dementia based on information obtained by telephone with the participant or their proxy, or an ICD-9 code of dementia appearing in any position in hospital discharge records[24] (N=1462). If participants with suspect dementia did not complete visit 5 or the TICS-M, their proxies were sought to complete a CDR. Suspect dementia status was available for all participants in ARIC.

For participants with suspect dementia, interviews were sought with proxy informants. The CDR was completed by telephone with informants familiar with the participant's current cognitive status (for living participants) or cognitive status 12 months prior to death. It covers six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). For deceased participants, interviewers were carefully instructed to focus on change in cognitive status occurring 12 or more months prior to death, and to avoid reports of pre-terminal cognitive decline. Because of the perceived limitation in attempting to reach proxies of participants who died more than 10 years prior to visit 5 and that few participants would be expected to have dementia prior to this date (mean age was 70), a CDR was sought only for participants who died after 2004.

Interviewers scored each of the six domains using a scale of 0 (no impairment), 0.5 (questionable), 1 (mild), 2 (moderate), and 3 (severe impairment). The CDR sum of boxes (total score) ranged from 0 to 18. The CDR was collected on 885 participants who did not attend visit 5 (N=575 with suspect dementia) and from 2856 who attended visit 5 (N=176 with suspect dementia).

Diabetes association with cognitive decline

We used mixed-effects models to accommodate the correlation between repeated measures over time. Time since baseline (visit 2) was modeled using a linear spline with a knot at six years (median time to visit 4). Our models included one random intercept and a random slope for each time spline term, and the random effects were assumed to be independent. The coefficients of interest were the interaction terms between diabetes and each time spline term, which indicate additional decline over time among persons with diabetes at baseline compared to those without. The models were adjusted for demographic, behavioral, and cardiovascular risk factors as have been previously used[25] (See Figure 2 legend).

Multiple imputation

Missing data can be classified as follows[26,27]: missing completely at random (MCAR) when missingness does not depend on either observed or unobserved data; missing at random (MAR) when, after conditioning on observed data, missingness does not depend on unobserved data; or missing not at random (MNAR), when missingness depends on unobserved data (such as unmeasured dementia status).

Multiple imputation replaces missing data with plausible values, and has been demonstrated to produce asymptotically unbiased estimates when missing data are MAR or MCAR[2,28]. To account for the uncertainty of the imputation and ensure correct standard error estimation, multiple imputations are performed[26]. Multiple imputation by chained equations (MICE) involves a series of imputation models, where each variable containing missing data is regressed on all other variables, including previously imputed missing variables[2,16,28,29]. The

flexibility of MICE to impute different data types (categorical, continuous, binary, etc) makes it an attractive tool for use in practice. We used 25 sets of imputations, although we observed little variation in estimates after 6-7 imputations (eFigure1). We estimated the association of diabetes with 20-year cognitive change by conducting analyses separately on each imputed dataset, and combined estimated coefficients and standard errors from each analysis using Rubin's rules[4].

The primary target of inference was the average trajectory of cognition while living, thus we imputed cognitive outcomes for persons lost to follow up whether living or dead. For living participants, scores were imputed at the median visit date. For deceased participants scores were imputed 6 months prior to death (and only for participants deceased after 2004). We also conducted analyses imputing scores only for participants alive at the start of visit 5, as such an estimand may be of interest for certain study questions. Finally, we examined the effects of imputing missing covariates or exposure on associations of interest (these participants are often excluded from analyses).

The imputation model for the global Z score at visit 5 included the same variables as the mixed-effects longitudinal model (described above) as well as variables collected from annual telephone calls, TICS-M, suspect dementia status, CDRs, and global Z scores from visits 2 and 4. From the most recently available (before visit 5) annual telephone call we included the following variables (all coded yes/no): coronary heart disease, diabetes status, hypertension status, history of stroke, self-reported poor health, and an indicator of whether a proxy familiar with the participant was needed for the telephone call. We selected these variables *a priori* based on knowledge of their association with probability of dropout and cognitive function. Interaction terms between suspect dementia and education, race-field center, prior visit Z scores, CDR, diabetes, and hypertension were also included. Interaction terms were needed because suspect dementia modified outcome relationships with prior cognitive performance and other covariates. For example, if a person with suspect dementia was found by CDR to have severe impairments, cognitive performance at an earlier exam may be less informative relative to current performance.

We examined including other visit-based variables collected in ARIC, e.g. from clinical chemistries, medical/health history, anthropometry, and medication survey. These additional variables did not improve the imputation or change the results of longitudinal analyses using these imputations.

Validation and simulation

We used two validation approaches. First, to validate imputations among participants alive at visit 5, we set to missing cognitive scores of a random sample of participants who attended visit 5, and then compared imputed with observed values. To validate an MCAR missingness assumption, we randomly selected 20% of participants and set their Z score to missing. To validate a MAR missingness assumption, we used a logit model to allow the probability of missingness to differ by the following baseline variables: age, race-center, education, diabetes, global Z from baseline, and diabetes*global Z from baseline. To validate imputed scores among participants deceased by visit 5, we used Z scores of participants who attended the Brain or Carotid MRI visits (2004-2006) and who died within 2 years after those visits. Since scores from these visits were not used in the imputation, this is validation based on independent information.

Second, we evaluated the performance of MICE using simulated Z scores and simulated patterns of missingness corresponding to MCAR, MAR, and MNAR. We retained the observed values of all covariates for individuals from the ARIC population, and simulated Z scores using a mixed-effects model that included age, race-field center, sex, body mass index, suspect dementia, diabetes, hypertension, and interaction terms suspect dementia*time, hypertension*time, current cigarette smoking*time, and diabetes*time, where time was model using spline terms (described above). Including suspect dementia was necessary to allow us to retain the correlations between risk factors and cognitive decline. Additionally, CDR data were specifically sought for persons with suspect dementia, so including it was necessary in generating “believable” Z scores, since we retained all observed covariates. Using this model, persons with hypertension, diabetes, or

smokers, by design, had accelerated cognitive decline. Coefficients of each variable and the random-effects parameters were chosen to be similar to values estimated from the cohort (these were estimated by fitting this same model using observed ARIC data). Simulation specifications are detailed in the Appendix.

To model probabilities of dropout and death, we created four scenarios reflecting different dropout mechanisms. Scenario 1 (MCAR) assumed death and dropout occurred completely at random. Scenario 2 (MAR) assumed the probabilities of death and dropout (separately) depended on prior visit global Z score, diabetes, hypertension, and smoking status modeled using a multinomial logistic regression. Scenario 3 (MAR for the extended set of variables, MNAR for variables included in primary analyses) assumed the probabilities of death and dropout depended on prior visit global Z score (visit 2 and 4), diabetes, hypertension, smoking status, suspect dementia, and a diabetes*suspect dementia interaction (suspect dementia collected around visit 5). Of the four scenarios, this scenario is most consistent with what we believe the true missingness pattern in ARIC to be. Scenario 4 (MNAR) assumed that dropout depended only on simulated visit 5 global Z scores (i.e. unobserved scores), and that death among dropouts was random with a probability of 0.4. For each scenario, we analyzed data using available-case analysis (mixed-effects modeling with maximum likelihood), MICE restricted to participants living at the time of visit 5, and MICE including both living and dead participants. We also calculated standard errors, bias, and confidence interval (CI) coverage (the percentage of simulations where the true association was contained in the 95% CI). Bias was calculated relative to a trajectory-up-to-death target of inference; comparison with a trajectory-among-those-living-for-visits target is in the Appendix.

Analyses were completed using Stata/SE Version 13.1 (StataCorp, College Station, TX).

RESULTS

Of the original baseline cohort, 55% did not attend visit 5, with approximately equal percentages due to death (29%) and dropout but living prior to visit 5 (26%); these percentages reflect the percentages of the original baseline cohort for whom imputation was done. Compared to participants who attended visit 5, participants who died by visit 5 tended to be older at baseline (age 60 vs 55 years), were more likely to have diabetes (24% vs 8%) and a history of stroke (4% vs 1%), and had worse baseline cognitive performance (**Table 1)**. Additionally, 15% of the deceased were suspected of having dementia, compared to only 4% among participants who attended visit 5.

Validation results based on observed data are shown in **Figure 1**. MICE produced unbiased imputed values regardless of whether an MCAR or a MAR approach was used to select the validation sample (**Figure 1, Panels A and B**). Additionally, imputed values were unbiased in subgroups defined by race, education, diabetes, cognitive performance at visit 4, or suspect dementia (not shown). Among both MCAR and MAR validation samples, and by these subgroups, mean differences between imputed and observed global Z ranged from -0.03 to +0.02 Z scores, and the r-squared from a linear fit model between observed and average imputed scores ranged from 0.65 to 0.68. As shown in **Figure 1, Panel C**, among 74 participants who died less than 2 years after attending the Brain or Carotid MRI Study, agreement between the imputed and observed global Z scores was excellent. The mean difference was -0.02 Z scores, and the r-squared was 0.70 from the linear fit model where observations were weighted relative to time since the Brain or Carotid MRI Study (calculated as 1/time, such that deaths closer to the visit received higher weights). Finally, **Figure 1, Panel D** shows the distribution of imputed scores at visit 5, by CDR availability, among persons with suspect dementia. The characteristics of participants without a CDR were similar to those with a CDR (eTable1). However, because the informant could not be located (and CDRs were not obtained), the average imputed scores were higher by 0.55 Z scores than the average imputed score for participants whose informant was

interviewed. This result implies that when a CDR could not be obtained, we had insufficient information with which to impute a plausibly low enough cognitive score.

Simulation results are in **Table 2**. In scenario 1 (MCAR), all methods yielded approximately unbiased estimates, as expected. When data were MAR (scenario 2), the available-case analysis and imputation for living participants yielded similar results: both slightly underestimated the target association. In contrast, imputation for living and deceased produced less biased results – a difference which may result from including suspect dementia in the data generating model but not the analytic model. In scenario 3, where death and dropout depended on suspect dementia, available-case analysis yielded a 23% bias, which was reduced to 12% with imputation for living participants, and 3% with imputation for all participants, both conservative. Available-case analysis had 95% CI coverage of 73%, compared to 94% using imputation. In scenario 4, where participants were missing based on their unobserved cognitive function, no method yielded unbiased results (bias ≈26%). Across all scenarios the bias in estimating the standard errors ranged from negligible to 20%. We also evaluated findings against a truth derived from only the living participants, an estimand which sometimes may be of interest. Here the available-case analysis was less biased (15% compared to 23%), and imputation in the living reduced the bias to 3% (eTable2, scenario 3).

Estimates of decline in persons with diabetes compared to those without are shown in **Figure 2**. Imputation of baseline covariates and exposure had no discernable effect on estimates, likely because only 4% of the baseline population was missing any covariates, and 1% was missing exposure. During the first 6 years of follow-up, persons with diabetes experienced an additional mean decline of 0.10 Z scores compared to those persons without diabetes. Imputation of cognitive performance had no discernable effect on estimates of 6-year change, as few participants dropped out or died during this time. During the next 14 years of follow-up (years 6-20), when most dropout occurred, we observe the effect of imputation on estimates of cognitive

decline. Using available-case analysis (i.e. no imputation), we estimated an additional mean decline of -0.08 Z scores in persons with diabetes compared to those without. Imputing the outcome yielded larger decline estimates, with similar results between imputation in only living participants (estimated additional decline -0.11 Z scores) and both living and deceased participants (estimated additional decline -0.12 Z scores). Imputation in the latter group yielded larger standard errors.

DISCUSSION

In this community-based cohort study, we used MICE to impute cognitive performance as the outcome for subsequent epidemiologic investigations. Validation analyses showed that MICE yielded unbiased imputations of cognitive performance for both living and deceased participants, with the exception that the procedure may not specify scores plausibly low enough for persons with suspect dementia whose informants could not be interviewed. We showed that estimates of the associations of diabetes with 20-year cognitive decline were substantially further from the null with the use of MICE, compared to analyses without imputation. Finally, simulations showed that when data are informatively missingness and related additional data are available, MICE may produce less biased estimates of associations of interest compared to available-case analysis. We note, however, several limitations to our simulations. First, suspect dementia was built into the data-generating model in our simulations but not included as a covariate in subsequent mixed models. Doing so highlights implications of unobserved covariates even in a MAR scenario: analyses including only participants living at visits and those also incorporating the deceased may target different estimands as a result. Second, simulation results depend on assumptions made about the generating, death, and dropout models. While we chose parameters for simulation models that we believe are realistic (coefficients obtained from models using observed ARIC data), results nonetheless depend on assumptions chosen.

Imputation for the entire study population, including those who died, attempts to represent the whole population's cognitive natural history up to (but not beyond) death. Thus, we imputed scores for the dead 6-months before death, with attempts made to ignore pre-terminal changes. While this approach has merits, it also has limitations. Imputations for dead participants are placed before death, which can occur during a wide time interval, while imputations for living participants are anchored to visits. Thus, the former imputation gives different statistical leverage to those who died. Our methods attempted to avoid any effect of accelerated pre-terminal decline, which though difficult, avoids potentially biasing the associations between outcomes and timing of observations. Similarly, estimating trajectories of cognitive function using data only at clinic visits of living participants has the advantage of being directly informed by observations timed independently of adverse outcomes. However, ignoring the stronger association of diabetes with cognitive decline attributable to dementia or death may fail to adequately represent the target population's natural history. The choice of when and for whom to impute the outcome deserves careful thought. While our study saw similar results under two scenarios (imputing only for living participants and imputing for living and deceased), others may not. Moreover, our study does not address the more controversial question of what the preferable approach is to dealing with the potential bias induced when attrition is due to death[30].

Though guidance regarding multiple imputation is available[2,16,29,31], less is known about its utilization in epidemiologic studies for imputing cognitive outcomes. Other methods, such as inverse probability weighting or likelihood-based approaches, are more common[32]. Multiple imputation may be ideal for handling missing data when valuable information is available only in a subset of participants, as is the case in our and other community-based cohort studies. More research is needed to determine if a combined approach using both imputation and inverse probability weighting in epidemiologic studies would yield improved estimates[33,34].

Advantages of MICE include its flexibility in imputing different data types (e.g. categorical, continuous, etc.), and relative ease of implementation using standard statistical

packages. A disadvantage of MICE may be its atheoretical nature. Specifically, the series of conditional models may lead to situations where the joint distributions are incompatible. However studies have shown that MICE appears to be generally robust against such incompatibility[1,28,35]. Though MICE produces unbiased estimates when missing data are MAR, in situations where data are missing based on unobserved information, such as unmeasured cognitive ability, MICE may produce biased estimates. In such scenarios an alternative approach, such as joint modeling, may be helpful; however, it may also be that analyses to explicate sensitivity of findings to the strength of non-ignorable associations are most optimal[36,37]. Finally, careful thought should be given to collection of alternative data to supplement the data collected at regular study visits, whether through proxies, phone calls, or other surveillance. Such supplemental data are invaluable to minimize informative missingness, although one should be careful to avoid differential information bias.

In summary, our results suggest that when informative data are available for participants who do not attend study visits, MICE is an effective tool for imputing cognitive performance as the outcome, and may improve assessment of cognitive decline.

Table 1. Participant baseline characteristics by vital status at visit 5

	Total	Attended visit 5	Alive, did not attend visit 5	Deceased by visit 5
N (%)	14,229	6,340 (45)	3,713 (26)	4,176 (29)
Age	57.0 (5.7)	55.1 (5.2)	57.4 (5.7)	59.8 (5.4)
Female, %	55.4	58.9	61.3	45.0
Black, %	24.7	22.6	22.9	29.5
HbA1c, %	5.8 (1.2)	5.6 (0.9)	5.7 (1.0)	6.2 (1.7)
Diabetes, %	13.6	7.5	12.2	24.2
Body mass index, kg/m^2	28.0 (5.4)	27.6 (5.1)	28.1 (5.5)	28.3 (5.8)
History of CHD, %	5.8	2.6	3.9	12.3
History of stroke, %	1.9	0.8	1.2	4.3
Hypertension, %	36.1	27.4	36.3	49.2
APOE e4 alleles, %				
0	69.1	71.1	68.9	66.3
1	28.2	26.6	28.5	30.5
2	2.6	2.3	2.6	3.2
Education, %				
Less than high school	21.9	14.7	23.5	31.4
High school	41.5	41.9	43.7	38.9
College/vocational	36.6	43.4	32.9	29.7
Smoking, %				
Current	22.4	16.2	21.0	33.1
Former	37.9	38.5	36.6	38.2
Never	39.7	45.3	42.4	28.7
Drinking, %				
Current	56.3	60.9	53.8	51.5
Former	21.2	17.1	21.0	27.6
Never	22.5	22.0	25.2	20.8
Measures of cognitive function				
Global Z	0.00 (1.00)	0.24 (0.93)	-0.01 (0.94)	-0.37 (1.04)
DWRT, words recalled	6.6 (1.5)	6.9 (1.5)	6.6 (1.5)	6.2 (1.6)
DSST, number completed	44.6 (14.2)	48.1 (13.5)	44.6 (13.4)	39.1 (14.4)
WFT, words generated	33.2 (12.5)	35.0 (12.2)	32.7 (12.1)	30.8 (12.8)
Suspected Dementia by Visit 5, %	10.3	4.2	15.6	14.7
CDR sum of boxes*	2.8 (4.7)	1.3 (2.4)	7.3 (6.8)	8.0 (6.9)
TICS-M	34.2 (7.4)	34.2 (7.7)	34.2 (7.3)	-

Values shown as % or mean (SD). All variables measured at visit 2 (1990-1992) except CDR, which was collect around the time of visit 5 (2011-2013) via contact with participants or a proxy. Suspected dementia was ascertained prior to visit 5 from hospitalization records with an ICD-9 code for dementia or from contact with participants or their proxy where cognitive impairment was indicated. * Available for a subset of participants, N=3741

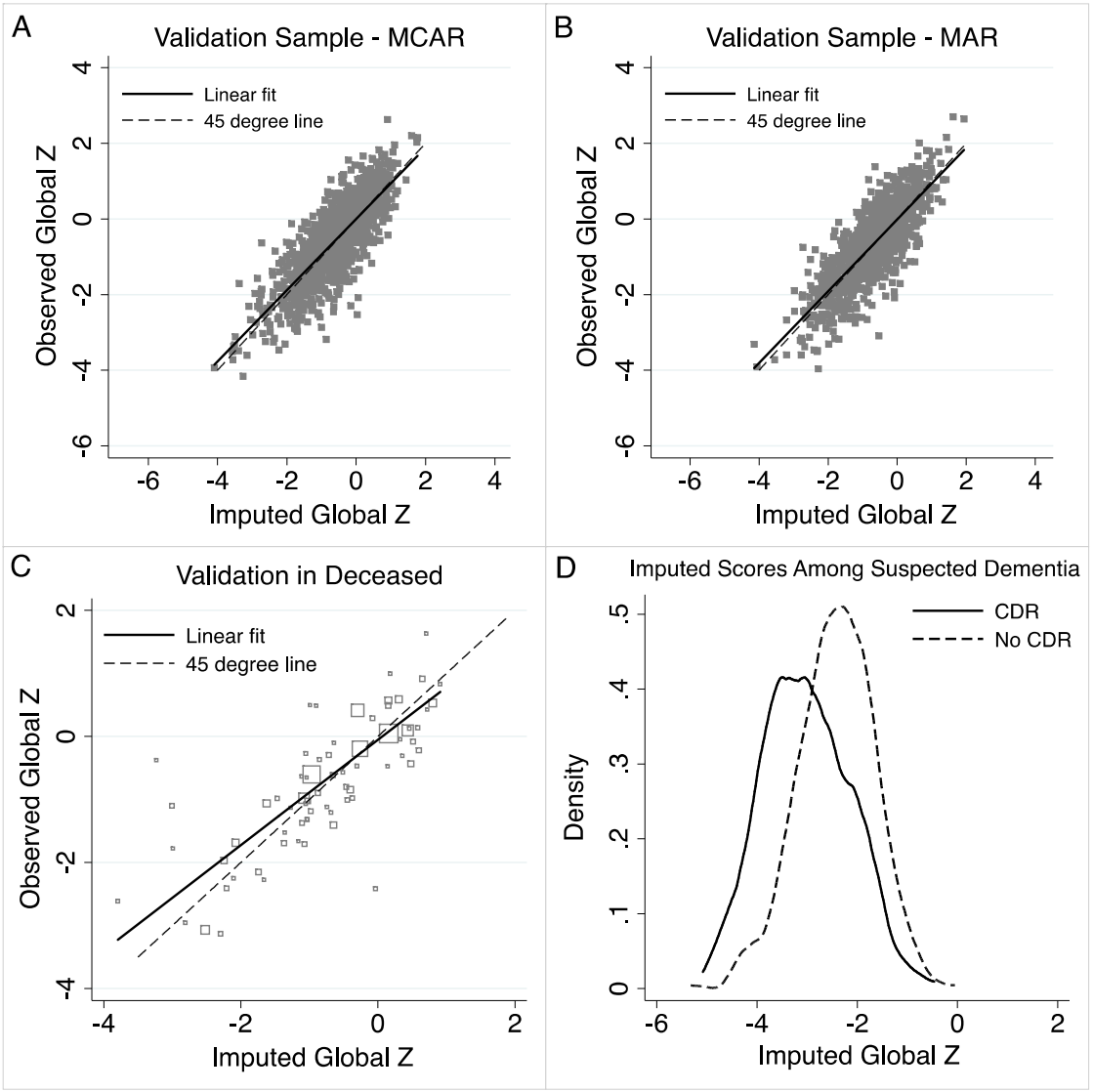
Abbreviations: CHD, coronary heart disease; DWRT, delayed word recall test; DSST, digit symbol substitution test; WFT, word fluency test; CDR, clinical dementia rating; TICS-M, modified telephone interview for cognitive status.

Table 2. Simulation results of estimated 20-year additional decline for persons with diabetes compared to those without

Scenario		Truth	Available case	Imputation	
		Living and deceased participants		Living participants	Living and deceased participants
1 MCAR	Mean (SE)	-0.237 (0.024)	-0.235 (0.035)	-0.231 (0.034)	-0.229 (0.033)
	Bias (%)	-	-0.001 (0%)	-0.005 (2%)	-0.007 (3%)
	Empirical SE	0.0202	0.0341	0.0322	0.0313
	CI coverage	-	100%	100%	98%
2 MAR	Mean (SE)	-0.237 (0.024)	-0.225 (0.042)	-0.221 (0.043)	-0.231 (0.044)
	Bias (%)	-	-0.012 (5%)	-0.016 (7%)	-0.006 (2%)
	Empirical SE	0.0202	0.0402	0.0389	0.0403
	CI coverage	-	96%	93%	96%
3 MAR for MICE, MNAR for available case	Mean (SE)	-0.237 (0.024)	-0.182 (0.042)	-0.208 (0.044)	-0.229 (0.047)
	Bias (%)	-	-0.055 (23%)	-0.029 (12%)	-0.007 (3%)
	Empirical SE	0.0202	0.0436	0.0448	0.0452
	CI coverage	-	73%	94%	94%
4 MNAR	Mean (SE)	-0.237 (0.024)	-0.168 (0.035)	-0.174 (0.037)	-0.175 (0.037)
	Bias (%)	-	-0.068 (29%)	-0.062 (26%)	-0.061 (26%)
	Empirical SE	0.0202	0.0341	0.0308	0.0307
	CI coverage	-	51%	65%	66%

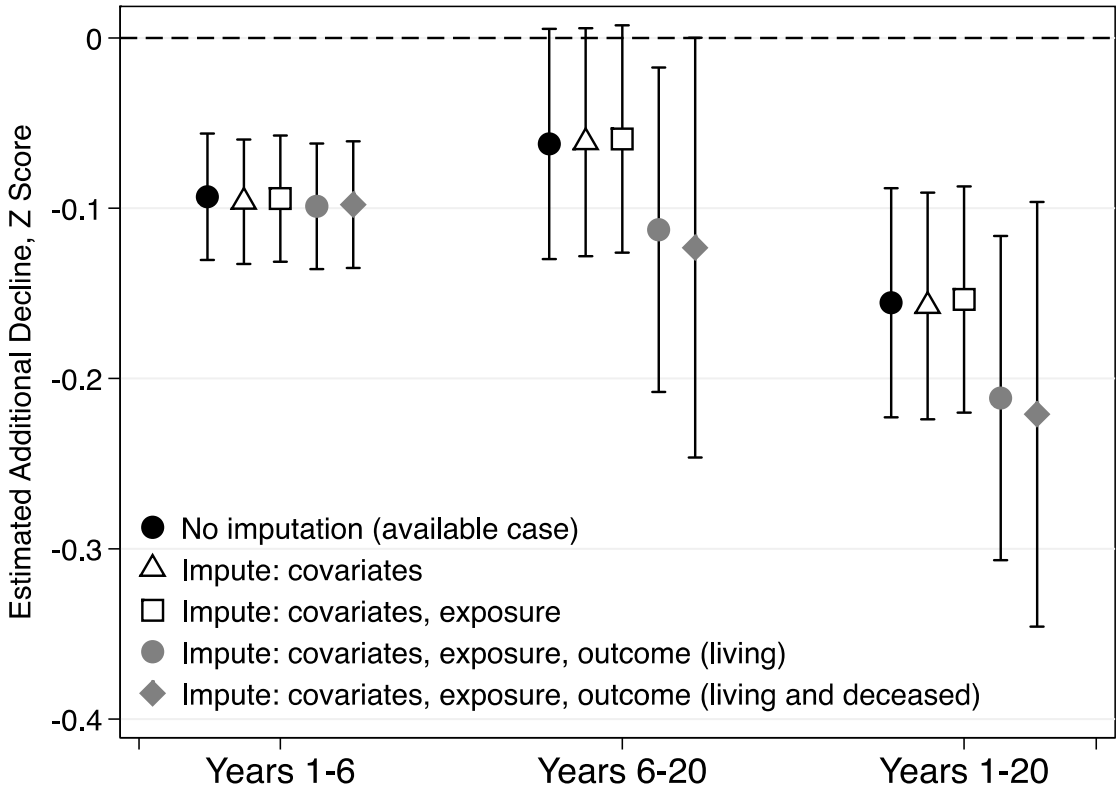
Mean effect is an average of 100 simulations. The standard error (SE) of the mean effect is the square root of mean variances across 100 simulations. Bias is calculated as the mean effect estimate from each method (available case, imputation in living participants, imputation in both living and deceased participants) minus the mean effect estimate from the truth. Negative values indicate underestimation of the true effect and positive values represent overestimation. Bias % is calculated as the estimated bias divided by the true effect (ie 0.005/0.237 = 2%). The empirical SE is the standard deviation of the mean effect across 100 simulations. CI coverage is the percentage of the simulations where the confidence interval for the estimated effect includes the true effect.
Scenario 1: Death and dropout simulated to be missing completely at random, with probabilities of 0.29 and 0.37, respectively, chosen to match proportions observed in ARIC. **Scenario 2:** Death and dropout simulated to depend on prior visit global Z score, diabetes, hypertension, and smoking status. **Scenario 3:** Death and dropout simulated to depend on prior visit global Z score, diabetes, hypertension, current smoking status, and suspected dementia. As a result, the "complete case", which uses a mixed model, is MNAR (suspect dementia not included in the mixed model), but MICE is MAR (suspect dementia is included for imputation). This scenario is more consistent with what we believe the true missingness pattern in ARIC to be. **Scenario 4:** Dropout simulated to depend on visit 5 global Z scores (i.e. unobserved scores), and death simulated to be missing completely at random.

Figure 1. Validation of multiply imputed global Z score using existing data



Legend:
Multiple imputation was done using chained equations, and 25 imputations were obtained and averaged for display in each plot. **Panel A:** 20% validation sample to simulate missing completely at random (MCAR) data. All participants had a 0.2 probability of being selected. If selected, participants' Z scores at visit 5 were set to missing and imputed. **Panel B:** 20% validation sample to simulate missing at random (MAR) data. Participants had varying probabilities of selection into the validation sample, with probabilities varying by education (less than high school, high school, greater than high school), race (black, white), diabetes (yes, no), or global Z score at visit 2 in the bottom 25th percentile (yes, no), and all interactions. If selected, participants' Z scores at visit 5 were set to missing and imputed. **Panel C:** Validation of imputed scores for participants who were deceased within 2 years of either the brain or carotid MRI visits, which took place 2004-2006 (N=74). Square size is inversely related to difference between visit date and death date (i.e. weight=1/time between visits), such that larger squares indicate death closer to the time of visit. Linear fit line is weighted using the inverse of difference between visit date and death date, and yielded an r-squared of 0.70. **Panel D:** Distribution of imputed scores among people with suspected dementia (N=1,462) by CDR status, adjusted for vital status (living/deceased).

Figure 2. Estimated additional decline in cognitive performance for persons with diabetes compared to persons without, by time period and amount of imputation



Legend:
Estimates and 95% CIs are for mixed-effects models using time since baseline as the time axis, modeled using a spline term with a knot at 6 years, the median time between visits 2 and 4. Random effects were random intercept and two random slopes, one for each time spline term. All models were adjusted for age, age squared, race-field center (Maryland (white race); Minnesota (white race); North Carolina (white race); North Carolina (black race); Mississippi (black race)), sex, education (less than high school; high school, high school equivalent, or vocational school; or college, graduate, or professional school), cigarette smoking status (current; former; never), alcohol consumption status (current; former; never), body mass index (kg/m^2), hypertension (yes or no), history of stroke (yes or no), apolipoprotein E ε4 genotype (0, 1, or 2 alleles). Interaction terms between the time spline terms and age, sex, race-field center, education, history of stroke, and apoliprotein E ε4 genotype were also included in the model. All covariates were assessed at visit 2 (baseline) except education, race, and sex (visit 1). 25 imputations were generated by chained equations. Sample sizes were as follows: No imputation: participants=13482, observations=29616; Imputation of covariates: participants=13901, observations=30567; Imputation of covariates, exposure: participants=14033, observations=30832; Imputation of covariates, exposure, and outcome for living participants: participants= 14151, observations=37854; Imputation of covariates, exposure, and outcome for living and deceased participants: participants=14151, observations=41479.

Chapter 3: Glucose peaks and the risk of dementia and 20-year cognitive decline

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ABSTRACT

Introduction: The risk of dementia and cognitive decline increase with increasing levels of hemoglobin A1c (HbA1c), a measure of average blood glucose. However, the association of cognition with glucose peaks is unclear. Here we examine the association of glucose peaks in midlife, measured by 1,5-anhydroglucitol (1,5-AG), with risk of dementia and 20-year cognitive decline.

Methods: Nearly 13,000 participants from the Atherosclerosis Risk in Communities Study were examined. Dementia was ascertained from community surveillance, visit-based cognitive tests, telephone calls with participants or their proxy, or from dementia codes on the death certificate. Cognitive function was assessed using three neuropsychological tests at three visits over 20 years, and was summarized as Z scores. We used Cox regression to examine the association between 1,5-AG and incident dementia, and mixed-effects models to model cognitive function over time. 1,5-AG was dichotomized at 10 μg/mL and examined within diabetes status and categories of HbA1c.

Results: Over a median of 21 years of follow-up, 1105 participants developed dementia. Among persons with diabetes, each 5 μg/mL decrease in 1,5-AG increased the risk of dementia by 16% (HR=1.16, p-value=0.032). For cognitive decline, among participants with diabetes and HbA1c <7%, those with glucose peaks had 0.19 more Z score decline over 20-years (p-value=0.162) compared to those without peaks. Among participants with diabetes and HbA1c ≥7%, those with glucose peaks had 0.38 more Z score decline compared to persons without glucose peaks (p-value=<0.001). We did not find associations between glucose peaks and cognition among persons without diabetes.

Conclusions: Participants with diabetes and glucose peaks had higher risk of dementia and greater cognitive decline over 20 years, compared to persons without glucose peaks, independent of HbA1c and other dementia risk factors. More studies are needed to determine if targeting

glucose peaks, in addition to average glucose, can reduce the risk of dementia and cognitive decline among persons with diabetes.

INTRODUCTION

Diabetes is an established risk factor for cognitive impairment, with evidence that diabetes affects performance in several cognitive domains and puts persons at increased risk of dementia[1–4]. However, the pathophysiologic mechanisms underlying these associations are unclear.

Hemoglobin A1c (HbA1c) is the standard clinical measure used for diagnosis and management of diabetes[5], and reflects mean blood glucose over the preceding 2-3 months. Several studies have shown that the risk of dementia and cognitive decline increases at higher levels of HbA1c[6–9]. However, HbA1c does not capture some aspects of glycemia, such as short-term variability or glycemic peaks, which may be particularly relevant for cognitive function.

1,5-anhydroglucitol (1,5-AG) is a monosaccharide similar to glucose in structure. In the presence of hyperglycemia (levels above the renal filtration threshold of approximately 180 mg/dL), 1,5-AG competes with glucose for renal re-absorption, which causes urine excretion and serum levels to fall. As a result, 1,5-AG reflects hyperglycemic peaks over a short period of time (7-10 days)[10,11]. Studies have documented that in persons with diabetes, 1,5-AG contributes to micro- and macro-vascular disease and death[12,13], independently of average blood glucose. Because of their effect on the vasculature, glucose peaks may be particularly important for cognitive function and dementia, but this association has not been widely explored.

Our aim was to characterize the prospective association between glucose peaks, as measured by1,5-anhydroglucitol, and 20-year cognitive decline and incident dementia in a community-based population. We hypothesized that glucose peaks, indicated by low levels of 1,5-AG, will be associated with higher risk of dementia and greater long-term cognitive decline, independent of average glycemia, as measured by HbA1c, and other risk factors for cognitive decline.

METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) study is a prospective cohort of 15,792 community-dwelling adults sampled from four U.S. communities: suburbs of Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. The first cohort examination took place 1987-1989, with three additional visits roughly three years apart. A fifth visit was completed 2011-2013. Institutional review boards at each study site reviewed and approved the study. Written informed consent was obtained from all participants.

The baseline for the current study is the second visit, which took place 1990-1992. Of the 14,348 participants who attended visit 2, we excluded participants who were neither black nor white (n=91) and participants missing 1,5-AG or HbA1c (n=1,246) giving a sample of n=13,007 for our analysis of incident dementia. For analysis of cognitive change, we further excluded persons missing cognitive testing at baseline (n=172) for a final sample of 12,835.

Measurement of 1,5-AG and HbA1c

1,5-AG was measured using a Roche Modular P800 system in 2012–2013 in stored serum samples originally collected at visit 2 (1990-1992). The interassay coefficient of variation was 5%, and the reliability coefficient using 610 masked duplicate samples was 0.99. Additionally, previous studies have shown that this assay is reliable in long-term stored samples.[14,15] HbA1c was measured in stored samples originally collected at visit 2 using high-performance liquid chromatography using the Tosoh 2.2 and the Tosoh G7.[16]

Definition of diabetes and prediabetes

Diabetes was defined on the basis of self-reported physician diagnosis, use of glucose-lowering medication, or measured HbA1c ≥6.5%. Among participants classified as not having diabetes using this definition, we defined prediabetes as an HbA1c in the range of 5.7-6.4%.

Assessment of incident dementia and cognitive function

Dementia was ascertained from community surveillance of hospitalizations, visit-based cognitive tests, telephone calls with participants or their proxy, or from dementia codes on the death certificate. For persons with dementia, the date was defined as the earliest of either: the first occurrence of a hospitalization with an ICD-9 code for dementia, date of death (if dementia codes were present on death certificate), date of telephone contact with participant or their proxy indicating dementia, or date of visit 5 in 2011-2013 (if participant had dementia at the visit but no earlier indication of dementia). Participants who attended visit 5 and were algorithmically classified as not having dementia[17] were censored at visit 5. Participants who did not attend visit 5 were censored at the last date where there was no known indication of dementia (telephone contact with the participant or their proxy or a hospitalization where no dementia was indicated).

Cognitive function was assessed at visits 2, 4, and 5 using 3 neuropsychological tests: Delayed Word Recall (DWR)[18], Digit Symbol Substitution of the Wechsler Adult Intelligence Scale-Revised (DSS)[19], and Word Fluency Test (WFT)[20]. Trained examiners administered the tests in a fixed order in a quiet room. Examiner performance was monitored by tape recording and reviewed locally and centrally to ensure consistency with testing protocols.

In the DWRT, participants were presented with 10 common nouns and asked to use each in a sentence. After completion of all 10 words, a second exposure to each word was given. After a five-minute delay, participants were given 60 seconds to recall the words, with scores ranging from 0-10. For the DSST, participants had 90 seconds to translate numbers (0-9) to symbols using a key. The score was calculated as the number of correctly translated symbols, with scores ranging from 0-93. Finally for the WFT, participants were given three 60-second trials to generate words beginning with the letters “F”, “A”, or “S”, excluding proper nouns. The total score for this test was the total number of words generated across the three trials.

We created a Z score for each test at each visit, standardized to visit 2, by subtracting the test mean (at visit 2) and dividing by the standard deviation (at visit 2). Next, we created a global composite Z score by averaging the Z score of the three tests and standardizing to visit 2.

Covariates

The following variables were evaluated as confounders: age; sex; race–field center (five categories: white persons from Minneapolis, Washington County, or Forsyth County; black persons from Forsyth County or from Jackson); education (less than high school; high school or vocational school; or college or above); cigarette smoking status (current, former, never); hypertension (yes/no, based on self-reported diagnosis, medication use or systolic ≥140 mmHg or diastolic ≥90 mmHg); history of coronary heart disease (yes/no); history of stroke (yes/no); body mass index; diabetes medication use (insulin, yes/no; sulfonylureas, yes/no); and apolipoprotein E4 (APOE4) genotype (coded as 0, 1, or 2 ε4 alleles). Education, race, and sex were evaluated at visit 1 (1987-1989). All other variables were assessed at visit 2.

Statistical analysis

We dichotomized 1,5-AG at 10 μg/mL, a cut-point recommended by the manufacturer and used in previous publications using these data[12,13]. This was done in persons without diabetes, in persons with diabetes and HbA1c <7%, and in persons with diabetes and HbA1c ≥7%, to create a 6-level exposure variable. We also modeled 1,5-AG continuously and using linear splines with knots at the 5th, 35th, 65th, and 95th percentiles.[21]

For analyses of incident dementia, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), and we used the Efron method to handle tied failure times. We verified the proportional hazards assumption using log-log plots. We used three models specified as follows: Model 1 was adjusted for age, race-field center, sex, and education; Model 2 was adjusted for the variables in Model 1 plus hypertension, history of stroke, history of coronary heart disease, cigarette smoking status, drinking status, and APOE4;

Model 3 was adjusted for the variables in Model 2 plus HbA1c, and was done stratified by pairs of 1,5-AG groups (3 separate models).

For analyses of change in cognitive function from baseline, we used mixed-effects models, which accounts for the correlation of repeated measures over time. We modeled time since baseline (visit 2) using a linear spline with a knot at six years (the median time between visits 2 and 4). Models included a random intercept and two random slopes for time (one for each spline term), and the three random effects were assumed to be independent. We adjusted for age, age squared, race-field center, sex, education, hypertension, history of stroke, history of coronary heart disease, APOE4, cigarette smoking status, drinking status, body mass index, and included interaction terms between each variable and time.

Missing data

477 participants at baseline (3.6%) had missing values for one or more covariates used in incident dementia or cognitive change analyses. We used multiple imputation by chained equations (MICE) to impute these missing baseline covariates. Additionally, for our analysis of cognitive decline, Z scores of participants dropping out of the study over time were also imputed using MICE as previously described (Chapter 2). Briefly, Z scores were imputed using information collected during and outside of study visits, including annual follow-up telephone calls, community surveillance of hospitalizations, the telephone interview for cognitive status, or retrospective dementia ascertainment, where the clinical dementia rating scale was given to the participant or a proxy. For participants alive at the time of visit 5, scores were imputed at the median visit date; for participants deceased by visit 5, scores were imputed 6 months prior to death. We calculated 10 imputations and results were combined using Rubin's rules.

Sensitivity analyses

We conducted a few sensitivity analyses to test the robustness of our results. First, for analyses of incident dementia, we restricted our study population to only individuals who had at least one hospitalization (N=10,646). This allowed us to examine if associations were due to

differential ascertainment of dementia between those with and without a hospitalization. This addresses the fact that persons with diabetes may be more likely to be hospitalized and thus receive a diagnosis of dementia. Second, we performed completely stratified analyses by diabetes and HbA1c categories. Third, to mitigate the possibility that participants with already low Z scores at baseline have less room to decline over time (floor effects), we excluded participants scoring in the bottom 5th percentile at baseline.

RESULTS

At baseline the average age was 57 years, 56% were female, and 24% were black (Table 1). Among persons with diabetes and HbA1c <7%, participants with 1,5-AG <10 μg/mL compared to those with 1,5-AG ≥10 μg/mL were less likely to be female (48% vs 58%), black (33% vs 43%), have less than a high school education (26% vs 36%), have a history of stroke (2.4% vs 5.1%), and be current smokers (18% vs 23%). HbA1c, body mass index, hypertension, and baseline Z scores were similar between these two groups, but fasting glucose was somewhat higher in those with 1,5-AG <10 μg/mL. Among persons with diabetes and HbA1c ≥7%, participants with 1,5-AG <10 μg/mL compared to those with 1,5-AG ≥10 μg/mL were less likely to be female (57% vs 67%), black (48% vs 58%), and have hypertension (61% vs 66%). They were also less likely to have 1 or 2 APOE e4 alleles (29% vs 36%) and had higher baseline Z scores (-0.55 vs -0.71).

Over a median follow-up of 21 years, 1105 participants developed dementia. Table 2 shows the association of baseline 1,5-AG levels, within diabetes and HbA1c status groups, with incident dementia. In fully adjusted models, compared to persons with well-controlled diabetes and 1,5-AG ≥10 μg/mL, persons with well-controlled diabetes and 1,5-AG <10 μg/mL had a 33% higher risk of dementia, though this was not statistically significant (p-value=0.285). Additionally, persons with poorly controlled diabetes and 1,5-AG <10 μg/mL had a 86% higher risk of dementia (p-value=0.011) compared to persons with 1,5-AG ≥10 μg/mL. In persons

without diabetes, the risk of dementia was not significantly higher in persons with 1,5-AG <10 μg/mL compared to those with 1,5-AG ≥10 μg/mL (HR = 1.05, p-value=0.754). We found similar, but attenuated results, when we stratified by diabetes and HbA1c, with additional adjustment for HbA1c (Supplemental Table 1), and when we restricted the population to only participants with at least one hospitalization (Supplemental Table 2).

The association between continuous values of 1,5-AG and dementia, in persons with diabetes, is shown in Figure 1. Each 5-unit decrease in 1,5-AG was associated with a 16% increased risk of dementia (HR=1.16, p-value=0.032). The association between 1,5-AG and dementia was similar when modeled using linear splines.

Figure 2 shows the estimated association between baseline categories of diabetes and 20-year cognitive decline. Among persons with diabetes and HbA1c <7%, persons with 1,5-AG <10 μg/mL had 0.19 greater Z score decline compared to persons with 1,5-AG ≥10 μg/mL (p-value=0.162). Among persons with diabetes and HbA1c ≥7%, persons with 1,5-AG <10 μg/mL had 0.38 greater Z score decline compared to persons with 1,5-AG ≥10 μg/mL (p-value<0.001). The association between diabetes and cognitive decline appeared to be modified by 1,5-AG status at baseline. Participants with 1,5-AG ≥10 μg/mL and diabetes, regardless of HbA1c status, had similar decline in cognitive function compared to persons with 1,5-AG ≥10 μg/mL without diabetes. However there was a graded association among persons with 1,5-AG <10 μg/mL, with a 0.26 Z score decline per diabetes and HbA1c category (Figure 2). We observed similar differences in 1,5-AG categories in analyses where we removed participants scoring in the bottom 5th percentile at baseline, however estimates were much less precise in these analyses (Supplemental Figure 1).

CONCLUSION

In this community-based study, we found that low levels of 1,5-AG, indicative of glycemic peaks, were associated with increased risk of dementia and greater cognitive decline

over 20 years. Specifically, 1,5-AG seemed to modify the association between cognitive decline and diabetes status. Persons with glucose peaks had the greatest decline, even if their average glycemic level, as measured by HbA1c, appeared to be well controlled (i.e. HbA1c <7%, although this was not statistically significant), while there was little difference in rates of decline by diabetes status and glycemic control in persons without glucose peaks.

The mechanisms by which diabetes leads to cognitive impairment are not well understood. It is thought that hyperglycemia, hypoglycemia, and oxidative stress, among other factors, play important roles[23], but less attention has been given to characterize the association with glycemic variability and debate on its usefulness in clinical practice is ongoing[24]. At the cellular level, fluctuations in glycemia have been shown to more adversely affect endothelial function and induce oxidative stress compared to sustained hyperglyceima[25–28], potentially leading to greater vascular damage and cognitive decline. A few studies using continuous glucose monitors (CGMs) have found associations between glycemic variability, higher mean amplitude of glycemic excursions (MAGE), and cognitive impairment and brain atrophy, independent of both mean levels of glycemia and hypoglycemic episodes[29–31], but long-term prospective studies have not been conducted.

Studies using data from CGMs have found moderate correlations between common measures of glycemic variability (e.g. mean amplitude glycemic excursions, postprandial glucose excursions) and 1,5-AG[32,33]. Additionally, studies have shown that 1,5-AG is associated with long-term micro- and macro-vascular outcomes, independently of HbA1c[12,13]. Glycemic variability is an aspect of glycemia that is not well captured by HbA1c, which is less sensitive than 1,5-AG to glycemic peaks. If glucose peaks in persons with diabetes contribute to long-term cognitive decline and dementia, above and beyond average hyperglycemia, it may also offer additional targets for prevention, though additional studies in this area are needed[24,34].

Our study has some limitations that should be considered when interpreting these results. First, ascertainment of dementia in participants not seen at the 2011-2013 examination was based

in part on ICD-9 codes, and insensitive method that may misclassify some cases. Second, we had only a single measure of 1,5-AG, although in ARIC it has been shown that total short-term variability of 1,5-AG (over a mean of 6 weeks) is intermediate between fasting glucose and HbA1c[35]. Third, we had relatively few participants in some of our exposure groups, which limited our statistical power in some analyses. Lastly, over 20 years of follow-up, a number of participants died or did not attend follow-up visits, potentially biasing associations of interest in a conservative direction. While we used validated methods to account for this drop out, including the use of auxiliary information collected to characterize participants' cognition during follow-up, these methods may not fully account for the effects of attrition. Our study also has a number of strengths, including a large sample size of nearly 13,000 adults, comprehensive assessment of confounders at baseline, well-characterized and validated neuropsychological tests for cognitive function and dementia assessment during follow-up, and a median follow-up of 21 years.

In summary, our study found that glucose peaks, as measured by 1,5-AG, were detrimental to cognitive function in persons with diabetes. 1,5-AG was associated with an increased the risk of dementia independently of mean glucose and other risk factors for cognitive decline. More research is needed to determine if targeting glucose peaks in the management of diabetes, in addition to mean glucose, can prevent or delay dementia and cognitive decline in persons with diabetes.

Table 1. Characteristics of study participants at baseline by diabetes status*, HbA1c, and 1,5-anhydroglucitol categories

		No Diabetes		Diabetes			
				HbA1c <7%		HbA1c ≥7%	
	Total	1,5-AG ≥10	1,5-AG <10	1,5-AG ≥10	1,5-AG <10	1,5-AG ≥10	1,5-AG <10
N (row %)	12,996	10,708 (82.4)	576 (4.4)	535 (4.1)	125 (1.0)	176 (1.4)	876 (6.7)
1,5-AG, μg/mL	17.6 (6.7)	19.5 (5.0)	7.4 (2.0)	17.9 (5.0)	6.9 (2.4)	15.4 (4.7)	3.3 (2.5)
Glucose, mg/dl	114 (44.1)	103 (11.2)	104 (18.2)	126 (24.0)	143 (44.2)	157 (36.3)	243 (85.1)
HbA1c, %	5.8 (1.2)	5.4 (0.4)	5.5 (0.4)	6.2 (0.5)	6.4 (0.5)	7.6 (0.8)	9.6 (1.9)
Prediabetes[†], %	17.0	19.1	26.9	-	-	-	-
Diabetes Medication, %							
Insulin[‡]	3.0	-	-	6.4	13.6	13.6	35.3
Sulfonylureas	3.8	-	-	14.0	28.8	26.1	38.7
Diabetes duration, years[§]	5.0 (2.8-11.9)	-	-	3.0 (2.7-8.9)	6.0 (2.8-14.7)	4.5 (2.8- 9.2)	5.9 (2.3-13)
Age, years	56.9 (5.7)	56.7 (5.7)	57.3 (6.0)	58.0 (5.8)	58.6 (5.6)	58.3 (5.7)	58.1 (5.7)
Female, %	56.3	55.6	65.6	58.1	48.0	66.5	57.2
Black, %	24.0	20.4	25.7	43.4	32.8	58.0	48.1
Education, %							
Less than high school	21.3	19.2	17.4	35.6	26.4	39.2	36.2
High school	41.9	42.6	40.4	36.3	40.0	38.1	38.2
College/vocational	36.9	38.2	42.3	28.1	33.6	22.7	25.6
Body mass index, kg/m^2	28.0 (5.4)	27.5 (5.1)	27.0 (5.0)	31.1 (6.1)	31.0 (5.8)	32.5 (6.5)	31.6 (6.1)
eGFR, mL/min/1.73 m^2	96.4 (15.7)	96.4 (14.4)	94.9 (18.4)	96.8 (18.3)	91.0 (25.2)	97.8 (20.3)	96.9 (21.9)
Hypertension, %	35.6	32.0	32.4	57.1	54.0	65.9	60.7
History of stroke, %	1.9	1.4	2.1	5.1	2.4	4.6	5.2
APOE e4 alleles, %							
0	69.4	69.5	66.4	69.5	73.4	64.5	71.0
1	28.0	28.0	31.3	26.1	23.4	32.0	26.8
2	2.6	2.6	2.3	4.4	3.2	3.5	2.2
Current smoker, %	22.1	22.7	16.8	23.0	18.4	21.1	18.0
Current drinker, %	56.6	59.9	57.1	39.1	43.2	31.3	33.3
Global Z score	0.00 (1.00)	0.08 (0.97)	0.05 (0.99)	-0.43 (1.01)	-0.48 (1.05)	-0.71 (0.98)	-0.55 (1.05)
Visit 5 status, N (%)							
Attended	5,869 (45.7)	5,172 (48.8)	275 (48.6)	150 (28.5)	33 (27.0)	45 (26.0)	194 (23.2)
Alive, did not attend	3,411 (26.6)	2,864 (27.0)	143 (25.3)	156 (29.7)	35 (28.7)	46 (26.6)	167 (19.9)
Deceased	3,550 (27.7)	2,569 (24.2)	148 (26.1)	220 (41.8)	54 (44.3)	82 (47.4)	477 (56.9)

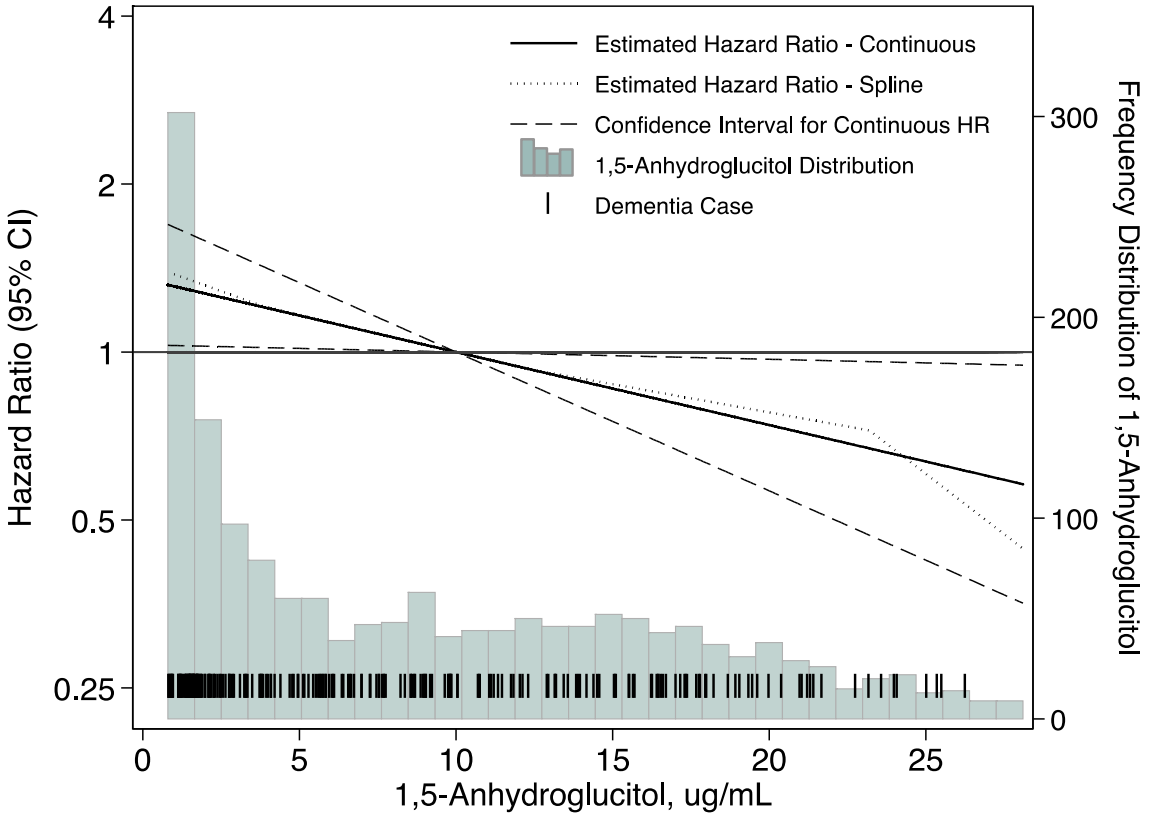
Values shown as mean (SD) or % unless otherwise indicated. * Diabetes was defined as a self-reported physician diagnosis of diabetes, use of glucose lowering medication, or an HbA1c ≥6.5% (by definition, persons in the "No diabetes" group have HbA1c <6.5%).
† Prediabetes was defined as HbA1c 5.7–6.4%.
‡ Includes insulin plus another oral medication.
§ Shown as median (25^{th} – 75^{th} percentiles).
Abbreviations: 1,5-AG, 1,5-anhydroglucitol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; APOE, apolipoprotein E.

Table 2. Adjusted HRs (95% CI) for the association of 1,5-anhydroglucitol categories with incident dementia by diabetes* status

		Events/N	Model 1 HR (95% CI)	p-value†	Model 2 HR (95% CI)	p-value†
No Diabetes						
	1,5-AG ≥10	829/10708	1 (reference)	0.962	1 (reference)	0.754
	1,5-AG <10	48/576	1.01 (0.75, 1.35)		1.05 (0.78, 1.40)	
Diabetes						
A1c < 7%	1,5-AG ≥10	60/535	1.34 (1.02, 1.75)	0.359	1.27 (0.97, 1.67)	0.285
	1,5-AG <10	19/125	1.71 (1.08, 2.70)		1.69 (1.07, 2.67)	
A1c ≥ 7%	1,5-AG ≥10	19/176	1.41 (0.89, 2.23)	0.020	1.31 (0.83, 2.07)	0.011
	1,5-AG <10	130/876	2.49 (2.06, 3.02)		2.44 (2.01, 2.97)	

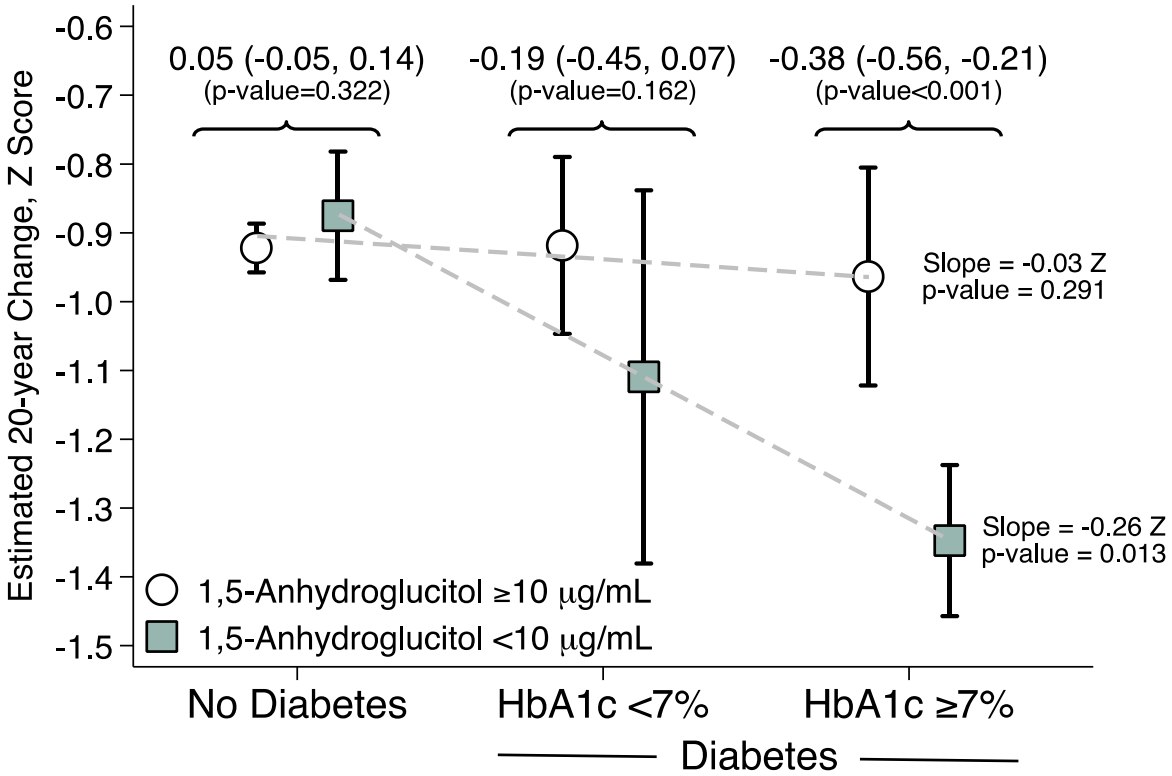
Model 1: Adjusted for age, sex, education, and race-center
Model 2: Adjusted for the variables in model 1 plus hypertension, history of stroke, history of coronary heart disease, cigarette smoking status, drinking status, APOE4
* Diabetes was defined as a self-reported physician diagnosis of diabetes, use of glucose lowering medication, or an HbA1c ≥ 6.5%
† p-values compare 1,5-AG ≥10 μg/mL to 1,5-AG <10 μg/mL within diabetes status and HbA1c category

Figure 1. Adjusted HRs (95% CI) for the association of 1,5-anhydroglucitol with incident dementia among persons with diabetes



Legend: Hazard ratios (HRs) were estimated using Cox proportional hazards regression among persons with diabetes (N=1659) with adjustment for age, race (black/white), sex, education, hypertension(yes/no), history of stroke (yes/no), history of coronary heart disease (yes/no), apolipoprotein E ε4 genotype (0, 1, or 2 alleles), and hemoglobin A1c. 1,5-anhydroglucitol was measured at baseline (1990-1992) and modeled continuously, with the reference point of 1,5-anhydroglucitol set at 10 μg/mL (the 60th percentile). We also modeled the association using linear splines with knots at the 5th, 35th, 65th, and 95th percentiles. Diabetes was defined as a self-reported physician diagnosis of diabetes, use of glucose lowering medication, or an HbA1c ≥6.5%. Median follow-up was 18 years and there were 217 cases of incident dementia.

Figure 2. Estimated association between baseline categories of diabetes and 20-year cognitive decline, by diabetes, HbA1c, and 1,5-Anhydroglucitol group



Legend: Estimates and 95% confidence intervals are from mixed-effects models with adjustment for age, age^2, race-field center, sex, education, cigarette smoking status, drinking status, hypertension, history of stroke, history of coronary heart disease, apolipoprotein E ε4 genotype, body mass index, and interactions between these variables and time. Time since baseline was the time axis, and was modeled with a linear spline with a knot at 6 years. A random intercept and two random slopes for time (one for each spline term) were included, and the three random effects were assumed to be independent. *Dashed lines indicate linear regression fit across 3 diabetes groupings (no diabetes, diabetes and HbA1c<7%, diabetes and HbA1c ≥7%) and 1,5-AG category. Decline indicates the estimated decline per categories and the p-value for the trend across categories.

Chapter 4: Factor Structure of the ARIC-NCS Neuropsychological Battery: An Evaluation of Invariance Across Vascular Factors and Demographic Characteristics

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ABSTRACT

Neuropsychological test batteries are designed to assess cognition in detail by measuring cognitive performance in multiple domains. This study examines the factor structure of tests from the ARIC-NCS battery overall and across informative subgroups defined by demographic and vascular risk factors in a population of older adults. We analyzed neuropsychological test scores from 6413 participants in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) examined in 2011-2013. Confirmatory Factor Analysis (CFA) was used to assess the fit of an *a priori* hypothesized three-domain model, and fit statistics were calculated and compared to one- and two-domain models. Additionally, we tested for stability (invariance) of factor structures among different subgroups defined by diabetes, hypertension, age, sex, race, and education. Mean age of participants was 76 years, 76% were White, and 60% were female. CFA on the *a priori* hypothesized three-domain structure, including memory, sustained attention and processing speed, and language, fit the data better (CFI=0.973, RMSEA=0.059) than the two-domain (CFI=0.960, RMSEA=0.070) and one-domain (CFI=0.947, RMSEA=0.080) models. BIC value was lowest, and QQ-Plots indicated better fit, for the three-domain model. Additionally, multiple-group CFA supported a common structure across the tested demographic subgroups, and indicated strict invariance by diabetes and hypertension status. In this community-based population of older adults with varying levels of cognitive performance, the *a priori* hypothesized three-domain structure fit the data well. The identified factors were configurally invariant by age, sex, race, and education, and strictly invariant by diabetes and hypertension status.

INTRODUCTION

Neuropsychological test batteries are designed to evaluate different areas of cognition in order to identify, track, and diagnose cognitive impairment and dementia (Hayden, Jones, et al., 2011). This motivates the grouping of neuropsychological tests to identify cognitive domains that may be differentially affected by disease pathology. Further, grouping cognitive tests into domains may reduce measurement error and may better facilitate testing of primary hypotheses regarding the possible etiology of various cognitive impairments (Gibbons, Bubb, & Brown, 2007; Silverstein, 2008).

Performance on neuropsychological tests may vary by age, global mental status, or for reasons unrelated to cerebral pathology, such as education level or cultural factors. It is important to determine if the underlying factors measured by cognitive tests are similar (invariant) across subgroups to ensure that observed variability in cognitive performance in different groups can be appropriately attributed to underlying cognitive abilities rather than to differences in the meaning of the tests. Such invariance analyses by demographics and cognitive status are important to establish and are commonly conducted (Hayden, Reed, et al., 2011; Mungas, Widaman, Reed, & Tomaszewski Farias, 2011; Park et al., 2012; Siedlecki, Honig, & Stern, 2008). Additionally, studies have examined invariance by genetic risk factors for Alzheimer's disease (AD) (Dowling, Hermann, La Rue, & Sager, 2010) with invariance among tests often varying by genetic risk factors in populations and by subgroups.

However, the examination of factor invariance by vascular risk factors, such as diabetes and hypertension, is less common. This is particularly important as hypertension and diabetes are common in the general population, and even more so in older adults and African Americans. Establishing the invariance of cognitive tests by vascular risk factors is vital for studies that aim to evaluate the associations of vascular risk factors or markers with cognitive decline and dementia.

Vascular dementia is the second most common type of dementia after AD, with the prevalence of pure vascular dementia about 10-15%. However, emerging evidence shows that most dementia may be a mix of both vascular dementia and AD pathology (O'Brien & Thomas, 2015). Studies have also shown that the clinical expression of dementia is larger in the presence of vascular disease, independent of the level of AD pathology (Jellinger & Attems, 2015; Snowdon et al., 1997). Hypertension and diabetes have been identified as risk factors for vascular dementia (Gorelick, 2004) and may be contributors to AD (de Bruijn & Ikram, 2014). Both of these risk factors are very common in older adults and, more importantly, are modifiable, providing potential means of intervention to prevent or delay the vascular contributions to dementia and AD.

The present study addressed two aims. The first aim was to explore the factor structure of the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) neuropsychological test battery using confirmatory factor analysis (CFA) for *a priori* hypothesized domains. The second aim was to explore the stability of the factor structure by demographic subgroups (defined by age, race, sex, and education) and vascular risk factors (diabetes and hypertension). The ARIC-NCS battery contains commonly used tests, and is very similar to the neuropsychological test battery from the National Institute on Aging Uniform Data Set (Morris et al., 2006; Weintraub et al., 2009).

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) Study is a bi-ethnic, community-based prospective cohort of 15,792 middle aged adults from four U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. ARIC participants were seen at four in-person visits roughly 3 years apart, from 1987-89 for visit 1, through 1996-98 for visit 4. A fifth visit took place from 2011-2013,

which included neuropsychological testing as part of the ARIC-NCS. 6538 participants attended visit 5, and 6501 completed the neurocognitive assessment. We excluded participants who were neither Black nor White (n=20) or who were missing all cognitive tests (n=68), giving a sample size of 6413 for the present study. Institutional review boards at each study site reviewed and approved the study; written informed consent was obtained from all participants.

Neuropsychological Assessment

The ARIC-NCS test battery included eleven of the neuropsychological tests recommended for inclusion in the National Institute of Aging's National Alzheimer's Disease Coordinating Center (NACC) Uniform Data Set Battery(Morris et al., 2006). Protocols for the tests were standardized and examiners were trained centrally. The tests were administered in a fixed order during one session in a quiet room.

We hypothesized that the tests represented three cognitive domains: Memory, Language and Verbal Fluency, and Sustained Attention and Processing Speed (SAPS), and that this grouping of tests best represents the data. This *a priori* hypothesized 3-domain structure was based in part on the presumed underlying neurological structures involved (Lezak, 2012) as well as findings from two studies, which also used tests comprising the NACC Uniform Data Set Battery, namely the Alzheimer's Disease Neuroimaging Initiative(Park et al., 2012) and the NACC study (Hayden, Jones, et al., 2011). Because validation necessitates not only verifying that a three-domain model well-characterizes the observed data, but also that models of lower dimensions do not suffice to this end, we additionally examined a one-domain model (all tests grouped together) and a two-domain model (a memory domain and a domain of the remaining tests, representing a language/SAPS combined domain). The tests, grouped according to our *a priori* hypothesized three-domain structure, are described below.

Memory Domain

Delayed Word Recall Test (DWRT): In the DWRT participants are presented with 10 common nouns that they are asked to use in a sentence. Two exposures to the words are given.

After a five-minute delay, participants are given 60 seconds to recall the words. The score for the DWRT is the number of words correctly recalled.

Logical Memory Test (LMT): In part 1, participants are read two short stories and are asked to recall the details immediately following each story. At the conclusion of Part 1, participants are told they will be asked again about the stories. Part 2 is completed after a filled delay of approximately 20 minutes, and consists of participants recalling details of the same stories from part 1. The metric for both parts is the number of correct details recalled, with a maximum score of 50 for each of the two parts. Here we present parts 1 and 2 separately, labelled as "LM 1" and "LM 2", respectively.

Incidental Learning: Incidental learning is based on the Digit Symbol Substitution Test (DSST). For the DSST, participants are not instructed to learn the digit-symbol pairs. Immediately following completion of the DSST, participants are asked to remember the symbols and corresponding digit-symbol pairs. The metric used for this test is the number of symbol-pairs correctly recalled, with a range of 0 to 9.

Language and Verbal Fluency Domain

Animal Naming: In this test, participants are asked to name as many animals as they can in 60 seconds. Names of extinct, imaginary, and magical animals are admissible. Credit also is given for breeds, different names for males, females, or infants of the same species (e.g. bull, cow, calf) as well as superordinate and subordinate (e.g. dog and terrier) for birds, reptiles, and insects. The score is the total number of animals generated.

Boston Naming Test (BNT): In the BNT, participants are shown a series of 30 line drawings, one at a time, and are given 20 seconds to name the object shown in each drawing. No hints or clues are provided. The variable used in our analysis is the number of drawings correctly identified.

Word Fluency Test (WFT): The WFT is a test of executive function and language. Participants are given 60 seconds to generate as many words as possible beginning with the

letters F, A and S (60 seconds for each letter), avoiding proper nouns. The WFT score is the total number of acceptable words generated for the three letters

Sustained Attention and Processing Speed (SAPS) Domain

Trail Making Test (TMT): The TMT is comprised of two parts, A and B. In part A, participants are presented with numbers 1-25 each in a separate circle and distributed haphazardly across a page, and are asked to draw lines connecting the numbers sequentially. Similarly in part B, participants are given a page containing numbers (1-13) and letters (A-L), and are asked to draw lines connecting the numbers and letters in sequential, but alternating, fashion. Time to completion is the metric used for both parts. Participant who take longer than four minutes to complete the test, or who make more than 5 errors, are given a maximum time of 240 seconds.

Digit Symbol Substitution Test (DSST): For the DSST, from the Wechsler Adult Intelligence Scale-revised (WAIS-R), participants are asked to translate numbers to symbols using a key. The score is the total number of numbers correctly translated to symbols within 90-seconds and the range of possible scores is 0 to 93.

Digit Span Backwards (DSB): In the DSB, participants are read a series of numbers increasing in length from 2 to 7 digits each and are asked to repeat each series backwards. There are two trials for each digit span length, giving a maximum score of 12.

Hypertension Assessment

Blood pressure was measured using an OMRON HEM-907XL automated blood pressure monitor. Following a five-minute quiet rest period, three blood pressure measurements were taken, and the second and third measurements were averaged. Hypertension was defined as an average (of the second and third readings) systolic blood pressure greater than 140, a diastolic blood pressure greater than 90, or self-reported blood-pressure lowering medication use.

Diabetes Assessment

Participants who had a measured haemoglobin A1c $\geq$ 6.5%, or who brought glucose-lowering medication to the study visit were classified as having diabetes. Additionally,

participants who self-reported a diagnosis of diabetes or glucose-lowering medication use during annual follow-up telephone calls prior to the study visit were also classified as having diabetes.

Statistical Analysis

For each cognitive test, we calculated standardized Z scores by subtracting the test mean from each participant's test score and dividing by the test standard deviation. For the Trail Making tests, Z scores were calculated after taking the log of the test scores. In addition, because a higher score on these tests indicates worse performance, we multiplied the Z score by -1 so that low Z scores indicated worse performance for all tests. Participants who did not complete a test due to difficulty were assigned a Z score of -2 as described in ARIC-NCS Manual 17 ("Manual 17. ARIC Neurocognitive Exam (Stages 2 and 3)," 2011).

Cronbach's alpha (Cronbach, 1951) was used to describe internal consistency reliability for test scores of each domain of the *a priori* hypothesized three-domain structure.

Factor Analysis

We examined the domain (factor) structure of the cognitive tests using the test-specific Z scores and confirmatory factor analysis (CFA). CFA was applied to the *a priori* hypothesized three-domain model (tests grouped as described above), the two-domain model, and the one-domain model. CFA models were fit using full-information maximum likelihood, which allows the inclusion of all participants who have at least one test score. Correlations between the errors of the two logical memory tests and the two trails making tests were included based on *a priori* expectation that the errors of these pairs of tests would be correlated as the tests themselves are highly related. The correlation between the trail making test part A and the digit symbol substitution test was included based on examination of model fit. Including these correlations allowed us to relax the assumption of conditional independence and resulted in improved model fit. Analyses were completed using Stata/SE 13.1 (StataCorp LP, College Station TX).

Configural invariance is met when the same tests are associated with the same factors in each group, and is evaluated using model fit statistics. We focused on configural invariance for

subgroups defined by age (dichotomized at the median age), sex, race, and education, using the three-domain structure. Education was grouped into three levels: less than high school (<HS), high school or vocational school (HS), or more than high school (>HS, includes any college or professional school). For hypertension and diabetes, we further examined metric, strong, and strict invariance. Metric invariance is met when factor loadings do not differ between subgroups. Strong invariance is met when factor loadings and intercepts do not differ between subgroups. Finally, strict invariance is met when factor loadings, intercepts, and residual variances do not differ between subgroups. The three error correlations (between the logical memory tests, trail making tests, and trails part A and digit symbol substitution) were unconstrained (allowed to vary) between subgroups for configural invariance, but were constrained for metric, strong, and strict invariance.

We examined five model fit statistics to assess both relative and absolute model fit. The Comparative Fit Index (CFI)(Bentler & Mooijaart, 1989; Bentler, 1990) compares the fitted model with a null model that assumes uncorrelated variables (i.e. the independence model). The Tucker-Lewis Index (TLI)(Marsh & Hau, 1996; Tucker & Lewis, 1973) is a similar measure of relative model fit that indicates improvement over the null model. CFI and TLI values range from 0-1, with values >0.9 indicating good model fit. The Root Mean Square Error of Approximation (RMSEA)(M. W. Browne & Cudeck, 1992; Steiger, 1989, 1990) and the Standardized Root Mean Residual (SRMR)(Steiger, 1989) assess absolute model fit. They are measures of the size of the model residuals and are insensitive to sample size and variable distribution. For RMSEA, values <0.05 indicate very good fit. For SRMR, values <0.08 indicate adequate fit, and values <0.05 indicate good fit. The Bayesian Information Criterion (BIC) (Raftery, 1995), is a criterion for model selection that adds a penalty for increasing model complexity and possible over-fitting of the data; the preferred model is the one with the lowest BIC. Additionally, changes in BIC values can be interpreted using grades of evidence described by (Raftery, 1995), where decreases in BIC >10 indicate very strong evidence to prefer the model with the lower BIC. Finally, for the

one-, two-, and three-domain models we calculated the correlation matrix residuals and created quantile-quantile (QQ) plots for the residuals of one- versus two-domain models and the two- versus three-domain models to further evaluate relative model fit (Michael W Browne, MacCallum, Kim, Andersen, & Glaser, 2002).

RESULTS

Characteristics of study participants and the distributions of the raw, non-standardized test scores are shown in **Table 1**. Participants' mean age was approximately 76 years, 76% were White, and 59% were female. The prevalence of vascular risk factors was high, with 74% of participants having hypertension, 33% diabetes, and 15% reporting a history of coronary heart disease.

The *a priori* hypothesized three-domain model with standardized factor loadings, correlations between the factors, and residual errors are shown in **Figure 1**. Correlations between the factors were relatively high, with values of 0.80, 0.82, and 0.85 for Memory/SAPS, Memory/Language, and Language/SAPS, respectively.

Fit statistics for the one-, two-, and three-domain models are shown in **Table 2**. Fit statistics for the one-domain model indicated good absolute fit (CFI=0.947, RMSEA=0.080), however they indicated worse fit than the two-domain model (CFI=0.961, RMSEA=0.070); the BIC value for the one-domain model was highest among the models considered. All fit statistics indicated better fit for the three-domain model (CFI=0.973, RMSEA=0.059), compared to the one- and two-domain models, and confidence interval for RMSEA excluded the confidence intervals for RMSEA from one and two-domain models. Of note, DSB had the lowest factor loading compared to all other tests, and compared to tests within SAPS. Thus, in a CFA where we excluded this test from our analyses, model fit statistics indicated even better fit (CFI=0.981, RMSEA=0.056). **Figure 2** shows the QQ plots for the correlation matrix residuals from models for two-domains versus one-domain (**Figure 2, Panel A**) and three-domains versus two-domains

(**Figure 2, Panel B**). Quantiles of the residuals indicate superior fit for the three-domain model compared to the two- and one-domain models.

Tables 3 and 4 show standardized factor loadings and fit statistics for the subgroup analysis of diabetes and hypertension, respectively, by each model of invariance. For both subgroups, fit statistics across all four models were similar and did not suggest deterioration in model fit as parameters were restricted to be similar across subgroups. Additionally, BIC values were lowest for the model with strict invariance; this model additionally had a BIC value that was more than 10 units lower than the other models, giving strong evidence to prefer it to the other models.

Standardized factor loadings and fit statistics of our demographic subgroup analyses are shown in **Table 5**. Model fit statistics for multiple group models based on age, sex, education and race were similar to the overall model, indicating configural invariance for these subgroups. RMSEA values ranged from 0.057 to 0.061 and SRMR values ranged from 0.033 to 0.037, both indicating configural invariance in each subgroup. Further exploration of invariance across these demographic factors indicated at least metric invariance across all demographic factors (**Online Tables 1-4**).

The internal consistency reliability of each domain was good, with alpha values of 0.81, 0.72, and 0.78 for the memory, language, and SAPS, respectively. Test scores within each domain had similar correlations with the domain, indicating consistency. For example, Animal Naming, Boston Naming, and Word Fluency test scores were correlated 0.827, 0.785 and 0.806 respectively with the Language and Verbal Fluency domain. An exception was scores of the DSB, which were less correlated with the SAPS domain than were test scores of Trails A, Trails B, and DSS (**Online Table 5**).

DISCUSSION

The growing interest in clarifying structural and functional associations in aging and disease in the context of the rapidly expanding minority and aging populations in the US motivates the need to demonstrate that the measures commonly used in clinical and epidemiologic studies have a stable structure (i.e., reflect the same construct) across potentially informative subgroups of vascular risk factors and demographics. Our *a priori* hypothesized three-domain structure based on our expectations from available published evidence (i.e. (1) Memory, (2) Language and Verbal Fluency, and (3) Sustained attention and Processing Speed), fit the data better than a one- or two-domain model. Additionally, we have established invariance in a diverse, community-based population of older adults, using a cognitive battery comprised of common tests. Our analyses of the stability of the factors across subgroups indicated configural invariance, meaning the same domains are being measured regardless of age, race, sex, or education. Further, examination of invariance by diabetes and hypertension status suggested substantial stability by these vascular risk factors. Similar domain structures and invariance between demographic factors have been previously reported (Dowling et al., 2010; Hayden, Jones, et al., 2011; Jack Jr. et al., 2012; Mungas et al., 2011; Siedlecki et al., 2008; Vemuri et al., 2012), however few studies have examined invariance by vascular risk factors.

Establishing invariance by vascular risk factors is particularly important, as diabetes and hypertension are common, especially so among Blacks and older adults. The ability to identify meaningful dimensions of cognitive function is relevant not only for diagnostic purposes but also for characterizing those at highest risk for cognitive decline and dementia (e.g., by race or other demographics) and informing underlying brain functional-structural relationships. Establishing invariance for these very common vascular risk factors in a diverse sample is an important prerequisite for addressing these types of questions.

Our study has both limitations and strengths. The first limitation is that we have only 3-4 tests to represent each cognitive domain, thus we may have limited precision to fully characterize

the domains. For example, DSB had the lowest factor loading compared to the other tests in the SAPS domain. This may indicate that DSB more finely measures an attention construct, whereas the other tests included in this domain relate more to processing speed and executive function. Second, Blacks in ARIC were recruited primarily from two communities, which may limit generalizing to other regions. However, the education backgrounds in Blacks from these centers are diverse, and the finding that the domain structure appears similar is encouraging. We note that while the alphas we estimated in our study are large enough for the purpose of making group-level comparisons, they are not large enough to make individual-level inferences (Nunnally & Bernstein, 1994).

A key strength of our study is the administration of a core of widely used tests, using a standardized protocol of centrally trained testers, to this large, diverse, community-based population. The battery of tests administered in ARIC-NCS is consistent with other large-scale studies, which provides for comparability across studies (Hayden, Jones, et al., 2011; Park et al., 2012; Siedlecki et al., 2008). Additionally, the use of full information maximum likelihood in the CFA analyses allowed us to include all participants. Lastly, the ability to infer appropriate conclusions about group differences on neuropsychological test performance presumes careful attention to the selection of tests, availability of relevant norms for comparison, and sensitivity to the measurement process/testing situation that may differentially impact performance. Our study goes one step further in addressing the robustness of the construct validity of the underlying cognitive domains under study.

The choice of the number of factors in a given factor analysis depends on a number of substantive considerations in addition to statistical fit. Previous studies have noted that persons with normal cognition tend to have less variability in their performance and a one-domain model is typically found (Gross, Jones, Fong, Tommet, & Inouye, 2014; Jones et al., 2010; Strauss & Fritsch, 2004). In contrast, individuals with impairment tend to have more heterogeneity in their performance and more than one factor may be needed to accurately capture status distinctions

because different cognitive abilities may deteriorate at different rates (Bakkour, Morris, Wolk, & Dickerson, 2013; Hayden, Reed, et al., 2011; Kanne, Balota, Storandt, McKeel, & Morris, 1998). In our study there was a persuasive improvement in fit for a three-factor model as compared to models with fewer factors or domains. Further, BIC values, which penalize for over-fitting, also indicated a three-domain model. However, we observed high correlations between the domains, ranging from 0.80-0.85, and the fit of the one-domain model was reasonable. Thus, using a global composite may have the advantage of greater overall reliability for characterizing individuals compared with composites of fewer tests, and perhaps greater sensitivity to the effects of the key causal factors that will be assessed in ARIC-NCS. The decision of the number of factors thus depends to some extent on the ultimate goal of the factor analysis.

In summary, in this community-based population of older adults, results from the CFA indicate that the ARIC-NCS battery may be summarized into three domains, and that these domains are stable across subgroups defined by age, race, education, diabetes or hypertension. For investigations into the contributions of vascular predictors (such as hypertension and diabetes) to cognition in older persons, it is vital to establish the invariance of cognitive domains by these risk factors. Our findings assure us, and future investigators, that one can use the same cognitive domain constructs to pursue questions regarding the vascular contribution to impairments. Using multiple indicators of cognitive performance may allow us to capture the general determinants of cognitive function, and average out method-specific and error components.

These results provide compelling evidence for the robustness of cognitive domains measured by our test battery. Our findings are encouraging for studies aiming to test hypotheses regarding the associations between midlife vascular factors and late-life cognitive impairment in diverse populations defined by age, race, education, and vascular risk factors.

Table 1. Characteristics of study participants, N=6413

	Total	25th, 75th percentile
Age, mean (SD)	76.2 (5.2)	71.9, 80.0
White, N (%)	4900 (76.4)	-
Female, N (%)	3770 (58.8)	-
Education, N (%)		
Less than high school	956 (14.9)	-
High school or GED	2672 (41.7)	-
College or vocational school	2774 (43.3)	-
Hypertension, N (%)	4744 (74.0)	-
Diabetes, N (%)	2091 (32.6)	-
History of coronary heart disease, N (%)	944 (14.7)	-
Cognitive Tests*		
Delayed Word Recall, words recalled	5.2 (1.9)	4, 6
Logical Memory 1, details recalled	21.5 (7.5)	16, 27
Logical Memory 2, details recalled	16.6 (7.9)	11, 22
Incidental Learning, symbol-pairs recalled	3.3 (2.3)	1, 5
Trails A, time (seconds)	50.2 (31.1)	33, 56
Trails B, time (seconds)	128.3 (60.6)	81, 165
Digit Symbol Substitution, symbols translated	37.8 (12.1)	29, 46
Digit Span Backwards, correct spans	5.5 (2.0)	4, 7
Animal Naming, animals generated	16.0 (5.1)	13, 19
Boston Naming, items identified	24.6 (5.5)	23, 28
Word Fluency, words generated	32.6 (12.4)	24, 41

* Sample size for individual tests vary; values reported as mean (SD)

Table 2. Fit statistics from confirmatory factor analyses by number of domains and domain definitions

	1 domain	2 domains	3 domains (all tests)	3 domains (without DSB)
CFI	0.947	0.961	0.973	0.981
TLI	0.929	0.946	0.962	0.971
RMSEA*	0.080 (0.077, 0.084)	0.070 (0.067, 0.073)	0.059 (0.056, 0.063)	0.056 (0.052, 0.060)
SRMR†	0.044	0.046	0.033	0.029
BIC	160,804	160,372	159,985	143,953

* RMSEA listed as estimate (90% confidence interval)

† SRMR calculated from models restricted to complete data

Abbreviations: DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index(>0.90 indicates good fit); RMSEA, root mean squared error of approximation(<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC).

Table 3. Standardized factor loadings and fit statistics for invariance models by diabetes

	Configural Invariance Variances constrained to 1, means to 0; intercepts, residuals, and factor loadings unconstrained		**Metric Invariance** Variances constrained to 1, means to 0, factor loadings invariant across groups; intercepts and residuals unconstrained		**Strong Invariance** Variances constrained to 1, means to 0, factor loadings and intercepts invariant across groups; residuals unconstrained		**Strict Invariance** Variances constrained to 1, means to 0, factor loadings, intercepts, and residuals invariant across groups	
Memory	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes	No Diabetes	Diabetes
DWR	0.64	0.66	0.64	0.65	0.64	0.65	0.64	0.65
LM 1	0.71	0.70	0.70	0.71	0.70	0.70	0.70	0.71
LM 2	0.73	0.73	0.73	0.73	0.73	0.73	0.72	0.74
Incidental Learning	0.63	0.67	0.63	0.67	0.63	0.67	0.64	0.65
Language								
Animal Naming	0.73	0.72	0.72	0.74	0.72	0.74	0.72	0.73
Word Fluency	0.65	0.70	0.65	0.69	0.66	0.70	0.67	0.68
Boston Naming	0.65	0.68	0.66	0.66	0.66	0.66	0.66	0.67
SAPS								
Trails A	0.67	0.72	0.68	0.69	0.68	0.69	0.69	0.69
Trails B	0.83	0.83	0.84	0.83	0.83	0.83	0.83	0.83
DSS	0.79	0.81	0.79	0.81	0.79	0.81	0.80	0.80
DSB	0.51	0.53	0.51	0.53	0.50	0.53	0.51	0.51
Fit statistics								
CFI	0.973		0.973		0.971		0.970	
TLI	0.961		0.964		0.965		0.969	
RMSEA*	0.060 (0.056, 0.063)		0.057 (0.054, 0.060)		0.056 (0.053, 0.059)		0.053 (0.050, 0.056)	
SRMR†	0.033		0.034		0.035		0.036	
BIC	158,916		158,868		158,852		158,783	

* RMSEA listed as value (90% confidence interval) † SRMR calculated from models restricted to complete data

Abbreviations: DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC).

Table 4. Standardized factor loadings and fit statistics for invariance models by hypertension

	Configural Invariance Variances constrained to 1, means to 0; intercepts, residuals, and factor loadings unconstrained		**Metric Invariance** Variances constrained to 1, means to 0, factor loadings invariant across groups; intercepts and residuals unconstrained		**Strong Invariance** Variances constrained to 1, means to 0, factor loadings and intercepts invariant across groups; residuals unconstrained		**Strict Invariance** Variances constrained to 1, means to 0, factor loadings, intercepts, and residuals invariant across groups	
Memory	No Htn	Htn	No Htn	Htn	No Htn	Htn	No Htn	Htn
DWR	0.67	0.63	0.66	0.64	0.66	0.64	0.66	0.64
LM 1	0.71	0.70	0.71	0.70	0.71	0.70	0.71	0.69
LM 2	0.73	0.72	0.74	0.72	0.74	0.72	0.74	0.72
Incidental Learning	0.63	0.65	0.64	0.64	0.64	0.64	0.66	0.64
Language								
Animal Naming	0.74	0.72	0.73	0.73	0.73	0.73	0.74	0.72
Word Fluency	0.65	0.68	0.66	0.67	0.66	0.67	0.68	0.67
Boston Naming	0.65	0.67	0.65	0.67	0.65	0.67	0.67	0.66
SAPS								
Trails A	0.69	0.69	0.70	0.68	0.70	0.68	0.69	0.68
Trails B	0.85	0.83	0.86	0.82	0.86	0.83	0.84	0.83
DSS	0.78	0.80	0.79	0.80	0.79	0.80	0.80	0.80
DSB	0.52	0.51	0.50	0.52	0.50	0.51	0.52	0.51
Fit statistics								
CFI	0.973		0.973		0.973		0.971	
TLI	0.961		0.965		0.967		0.970	
RMSEA*	0.059 (0.056, 0.063)		0.056 (0.053, 0.060)		0.055 (0.052, 0.058)		0.052 (0.049, 0.055)	
SRMR†	0.034		0.034		0.036		0.036	
BIC	158,441		158,378		158,342		158,277	

* RMSEA listed as value (90% confidence interval) † SRMR calculated from models restricted to complete data

Abbreviations: Htn, hypertension; DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC).

Table 5. Standardized factor loadings and fit statistics by subgroups of age, sex, race, and education

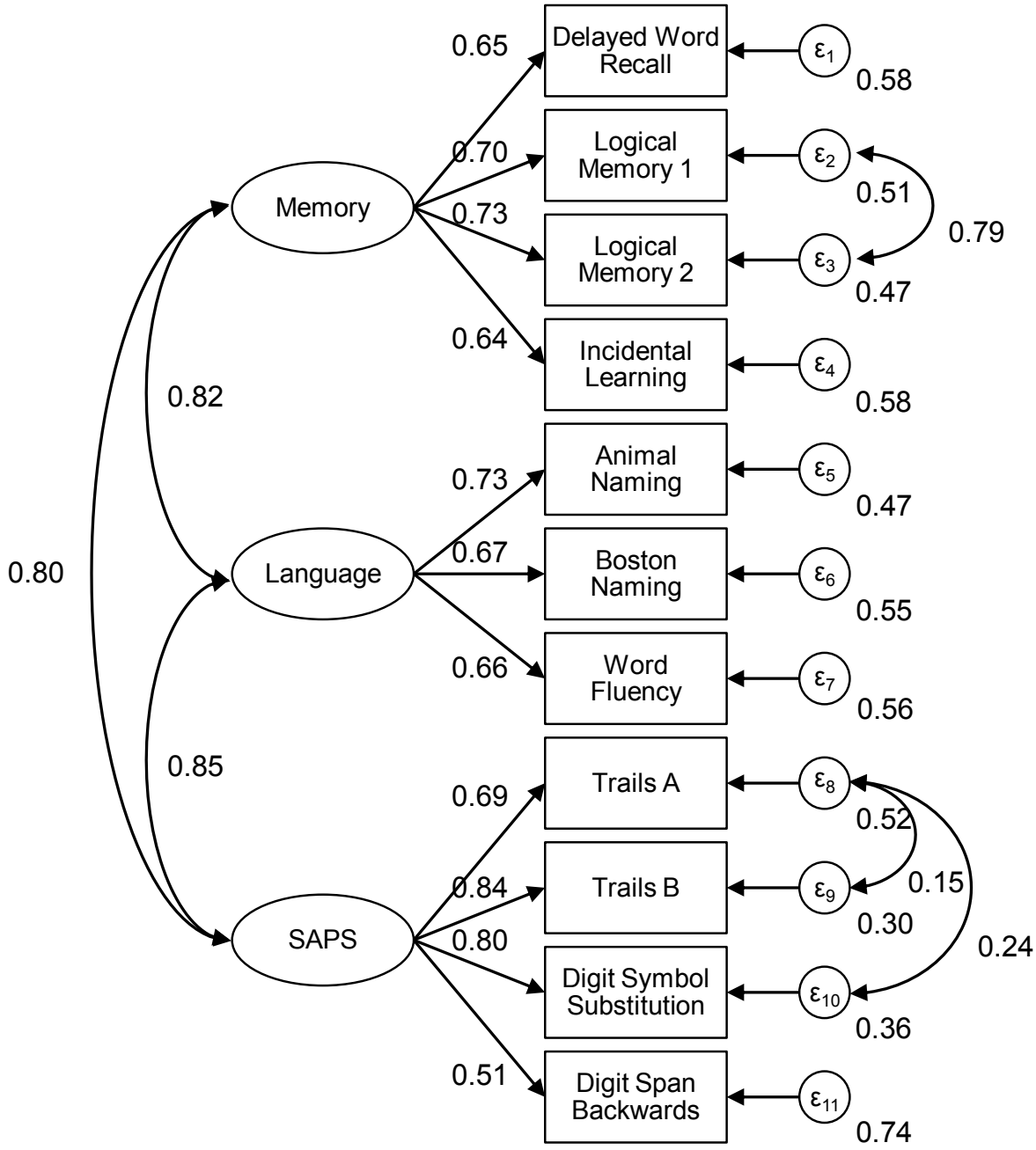
	Age		Sex		Race		Education		
Domain/Test	<75	≥75	Male	Female	White	Black	<HS	HS	>HS
Memory									
DWR	0.57	0.65	0.62	0.67	0.64	0.68	0.68	0.63	0.66
LM 1	0.62	0.73	0.68	0.72	0.69	0.74	0.67	0.65	0.65
LM 2	0.65	0.75	0.71	0.74	0.72	0.75	0.70	0.69	0.69
Incidental Learning	0.60	0.65	0.65	0.64	0.64	0.65	0.59	0.62	0.64
Language									
Animal Naming	0.67	0.73	0.71	0.74	0.73	0.74	0.70	0.69	0.76
Word Fluency	0.71	0.67	0.68	0.66	0.64	0.77	0.73	0.58	0.59
Boston Naming	0.61	0.66	0.64	0.70	0.63	0.77	0.62	0.61	0.59
SAPS									
Trails A	0.62	0.68	0.67	0.71	0.66	0.79	0.69	0.69	0.61
Trails B	0.80	0.83	0.83	0.85	0.84	0.84	0.77	0.81	0.81
DSS	0.76	0.79	0.82	0.81	0.78	0.87	0.81	0.78	0.75
DSB	0.51	0.50	0.53	0.50	0.49	0.58	0.50	0.43	0.45
Fit statistics									
CFI	0.971		0.976		0.972		0.970		
TLI	0.958		0.965		0.960		0.956		
RMSEA*	0.059 (0.056, 0.062)		0.057 (0.054, 0.061)		0.061 (0.058, 0.065)		0.059 (0.056, 0.063)		
SRMR†	0.035		0.033		0.034		0.037		

* RMSEA listed as value (90% confidence interval)

† SRMR calculated from models restricted to complete data

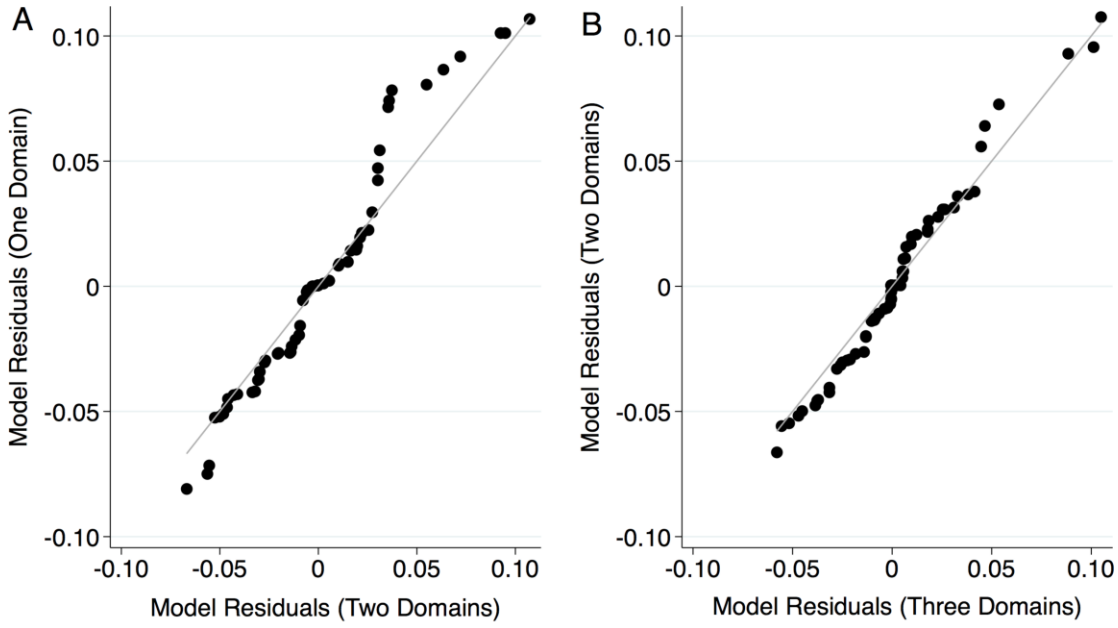
Abbreviations: HS, high school; DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit).

Figure 1. Confirmatory factory analysis model derived from *a priori* hypothesized domain structure



Legend: Latent factors are shown in ovals, measured tests are shown in rectangles, and error terms are shown in circles. Values shown between factors and between factors and tests are correlations. Values along curved and straight arrows are correlations, while values shown outside the circles for ε_1-ε_{11} are residual variances.

Figure 2. Quantile-quantile plot of correlation matrix residuals comparing one- versus two-domain models and two- versus three-domain models



Legend: Each model fit implies estimates for all correlations among neuropsychological tests. Residuals from model fits (observed-estimated) are shown as qq-plots in which percentiles of the residuals from the two models are plotted against one another (axes are labeled with original units of the residuals). Equivalent fits appear as equivalent distributions of the deviations between fitted and observed values, hence lie along the y=x line (shown as solid line). Panel A: residuals from the one-domain model plotted versus residuals from the two-domain model. Panel B: residuals from the two-domain model plotted versus residuals from the three-domain model. In both panels, there is systematic deviation from the y=x line with residuals from models with lower numbers of domains more dispersed than those from models with higher numbers of domains, indicating inferior fit.

Chapter 5: Diabetes, glucose peaks, and the prevalence of cognitive impairment in memory, language, and executive function among older adults

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ABSTRACT

Objective: To characterize the prevalence of cognitive impairment among older adults by diabetes status, diabetes duration, glucose control (assessed by hemoglobin A1c, HbA1c), and glucose peaks (assessed by 1,5-anhydroglucitol, 1,5-AG).

Research Design and Methods: We conducted a cross-sectional study of 5,746 participants aged 67-90 years from the Atherosclerosis Risk in Communities Study (2011-2013), and characterized cognitive impairment in memory, language, and executive function domains. We categorized HbA1c among persons without diagnosed diabetes as low-normal (<5%), normoglycemic (5-5.6%), prediabetes (5.7-6.4%), and undiagnosed diabetes (≥6.5%), and among persons with diagnosed diabetes by glycemic control (HbA1c<7% vs ≥7%). We examined glucose peaks (1,5-AG<10 μg/mL vs ≥10) within each HbA1c category.

Results: Participants with diabetes were 13%, 20%, and 11% more likely to have impairment in memory, language, and executive function, respectively, compared to participants without diabetes. For executive function, we observed the greatest prevalence of cognitive impairment in the following groups: low-normal HbA1c (31%), undiagnosed diabetes (34%), in persons with diabetes duration >10 years (30%), and in persons with diabetes and HbA1c≥7% (34%), compared to a prevalence of 20% in the normoglycemic group. Among persons with diagnosed diabetes and HbA1c≥7%, those with glucose peaks compared to those without were 1.41 times more likely to have cognitive impairment (p-value=0.018).

Conclusions: The prevalence of cognitive impairment in older adults with diabetes is high. More research is needed to determine if reducing HbA1c or glucose peaks in this group can improve cognitive function, and if screening for cognitive impairment among persons with diabetes can help to better individualize treatment.

INTRODUCTION

The U.S. population is rapidly aging. In 2010, 14% of the population was 65 and older and the number is expected to nearly double, reaching more than 70 million, by 2030[1]. In this population of older adults, the prevalence of diabetes and prediabetes is 22% and 24%, respectively[2]. Additionally, the prevalence of dementia among persons aged 71 and older has been estimated at 13.9%, and increases with age, with an estimated prevalence of 37.4% among persons 90 years and older[3]. Further, an estimated 22% have cognitive impairment without dementia[4]. Studies have shown that diabetes affects several cognitive domains, including processing speed, memory, executive function, and attention, and increases the risk of dementia[5–7]. The number of adults with both diabetes and cognitive impairment is growing, and represents challenges for patient care, as domains typically associated with diabetes are most relevant for its management. However the prevalence of cognitive impairment in older adults with diabetes, and its association with glycemic control, is relatively uncharacterized.

Hemoglobin A1c (HbA1c) is recommended for use in the diagnosis of diabetes, and is the standard measure used in the clinical monitoring of glycemic control in persons with diabetes, reflecting glycemic exposure over the previous 2-3 months[8]. HbA1c is a measure of average glucose and does not reflect short-term glucose fluctuations, which are common among persons with diabetes, even those with good glycemic control[9]. Fluctuations in glucose and glucose peaks may be important aspects of glycemia that contribute to the development of complications in type 2 diabetes[10,11].

1,5-anhydroglucitol (1,5-AG) is a biomarker that provides information about daily fluctuations in glucose[12–14]. 1,5-AG is a monosaccharide similar to glucose in structure. When serum glucose concentrations rise above the renal threshold, 1,5-AG competes for renal reabsorption and is excreted, causing serum levels to fall. Thus, low levels of 1,5-AG are an indication of the presence of glucose peaks over the preceding 1-2 weeks[15,16]. Studies have documented that 1,5-AG is associated with higher risk of micro- and macro-vascular disease and

death in persons with diabetes[17,18], independently of HbA1c. Mean levels of glycemia have been associated with cognitive function[19], but less is known about the association of cognition with glucose peaks. Glucose peaks, in addition to average glycemia, may be particularly important for characterizing the heterogeneity in cognitive function among older adults.

The objective of this study was to characterize the prevalence of cognitive domain impairment among older adults, and to examine differences by diabetes status, diabetes duration, glucose control assessed by HbA1c, and glucose peaks assessed using 1,5-AG.

RESEARCH DESGIN AND METHODS

Study population

The Atherosclerosis Risk in Communities Study (ARIC) is a prospective, community-based cohort study. A total of 15,792 adults age 45-64 were recruited from four communities in the US: selected suburbs of Minneapolis, Minnesota; Jackson, Mississippi; Washington County, Maryland; and Forsyth County, North Carolina. Participants attended four visits, each roughly three years apart, beginning in 1987-1989. A fifth visit was conducted 2011-2013, and is the baseline for the present study.

Of the 6,538 participants who attended visit 5, we excluded participants who were neither black nor white and the small number of black participants from the Minnesota and Washington County sites (n=42), and those who did not complete any neuropsychological tests (n=750), for a final sample size of 5,746. To calculate adjusted prevalence estimates or ratios, we additionally excluded participants missing covariates of interest (n=239). All participants gave written informed consent and institutional review boards at each site approved the study.

Measurement of HbA1c and 1,5-AG

HbA1c was measured using a Tosoh G7 automated high-performance liquid chromatography analyzer (Tosoh Bioscience, Inc, South San Francisco, CA) standardized to the

Diabetes Control and Complications Trial assay. 1,5-AG was measured in serum using the GlycoMark 1,5-AG reagent on a Roche Modular P800 system (Roche Diagnostics Corporation).

Definitions of diabetes, glycemic control, and diabetes duration

We defined diabetes (yes/no) as a self-reported physician diagnosis of diabetes, use of glucose-lowering medication, or an HbA1c ≥6.5%. We defined diagnosed diabetes (yes/no) based on a self-reported physician diagnosis of diabetes or current glucose-lowering medication use.

Among participants without diagnosed diabetes, HbA1c was divided into four groups: <5% (low-normal), 5-5.6% (normoglycemic), 5.7-6.4% (prediabetes), and ≥6.5% (undiagnosed diabetes). Among participants with diagnosed diabetes, we dichotomized HbA1c into <7% or ≥7%. To examine associations with glucose peaks, we dichotomized 1,5-AG within the HbA1c categories described above. As there are currently no established cut-points for 1,5-AG, we dichotomized at 10 μg/mL (<10 versus ≥10 μg/mL). Concentrations less than 10 μg/mL are associated with glucose peaks above the average renal threshold (~160-180 mg/dL)[15,20], and have been used previously in these data[17,18].

Starting with the original study visit (1987-1989), diabetes was ascertained at each study visits and on annual telephone calls. Duration was calculated as the date of the visit 5 exam minus the date of the first participant report of diabetes or diabetes medication use, either from study visits or telephone calls. For participants who first reported diabetes at visit 5, we used the date of their most recent contact without a report of diabetes to calculate duration. Participants who reported diabetes at the original study visit were classified as having diabetes for 25+ years.

Neuropsychological test assessment of cognitive function

We included eight tests from the neuropsychological test battery administered at visit 5: delayed word recall test (DWRT), digital symbol substitution test (DSST), word fluency test (WFT), logical memory parts 1 and 2 (LM-1, LM-2), trail making test parts A and B (TMT-A, TMT-B), and animal naming test (ANT). The cognitive tests are described in the Supplement. We grouped the tests into three domains representing memory, language, and executive function. The

memory domain included DWRT, LM-1, and LM-2, the language domain included WFT and ANT, and the executive function domain included DSST, TMT-A, and TMT-B.

For each test, raw test scores were converted to Z scores by subtracting the test mean from each participant's score and dividing by the test standard deviation. To calculate domain Z scores, tests within each domain were averaged and converted to Z scores by subtracting the domain mean and dividing by the domain standard deviation.

Definition of cognitive domain dysfunction

Dysfunction in each cognitive domain was calculated using raw scores from each neuropsychological test and age-, race-, and education-adjusted norms calculated from a sample of ARIC participants free of clinical or subclinical neurological disease or latent dementia[21]. For each test, scores more than 1.5 standard deviations below these norms, a commonly used criterion[22], were classified as failure. We defined cognitive domain dysfunction as failure on 2 or 3 tests of the memory and executive function domains, and 1 or 2 tests in the language domain.

We also defined cognitive dysfunction in a manner similar to clinical practice, based on expert review of participants' medical information to diagnose mild cognitive impairment (MCI) and dementia[23]. Two diagnostic reviewers independently reviewed neuropsychiatric information, medical and family history, participant or proxy report of memory complaints, results from the physical examination and laboratory values, imaging information from brain MRI at the 2011-2013 exam, and use of certain medications by participants. If the two reviewers did not agree on a diagnosis, the case was assigned to a third independent adjudicator. There were 1,186 cases of MCI and 160 dementia cases in our study population, which we grouped and defined MCI/dementia.

Statistical analysis

We used Poisson regression with robust variance estimation to estimate the prevalence of cognitive dysfunction. For models adjusted for covariates, the prevalence of cognitive dysfunction was calculated at the mean of each of the covariates. We estimated the prevalence of

cognitive dysfunction by diagnosed diabetes and HbA1c category, and among persons with diagnosed diabetes, we examined cognitive dysfunction by diabetes duration. We also estimated the prevalence of cognitive dysfunction by glucose peaks within each HbA1c category.

To examine differences between prevalence estimates, we calculated prevalence ratios (PRs) adjusted for age, race, sex, education (less than high school; high school or vocational; college or professional school), hypertension (yes/no, defined as measured systolic blood pressure ≥140 mm Hg, or measured diastolic blood pressure ≥90 mm Hg, or use of blood-pressure lowering medication), history of coronary heart disease (yes/no), history of stroke (yes/no), drinking status (current; former; never), cigarette smoking status (current; former; never), and apolipoprotein E ε4 (APOE4) genotype (0,1, or 2 alleles). In analyses comparing 1,5-AG groups (<10 μg/mL versus ≥10 μg/mL) within HbA1c category, we additionally adjusted for HbA1c. In sensitivity analyses we also examined the individual domain Z scores (continuous variables), which provided enhanced power to observe associations since the dichotomizing of cognitive function can result in a loss of information.

All analyses were conducted using Stata/SE version 14.1 (College Station, TX). All p-values reported are two-sided and $p<0.05$ was considered statistically significant.

RESULTS

The mean age was 76 years, 59% of participants were female, 80% were white, and 33% had diagnosed diabetes (**Table 1**). Among persons with no diagnosed diabetes, we observed similar differences across the four HbA1c categories for race, education, hypertension, history of coronary heart disease, history of stroke, and cognitive scores. Persons without diabetes and HbA1c <5% ("low-normal" group) had poorer cardiometabolic profiles, lower cognitive test scores, and were much more likely to have 1 or more APOE4 risk alleles as compared to persons without diabetes and HbA1c of 5.0-5.6%. These participants also had a decline in HbA1c values from midlife, compared to an increase across all other groups (**Supplemental Table 1**).

Overall, 23% of participants had cognitive domain dysfunction in memory and executive function, compared to 12% in language. We observed the most cognitive dysfunction in the memory and executive function domains among participants without diagnosed diabetes with low-normal HbA1c, and among participants with diagnosed diabetes and HbA1c ≥7% (**Figure 1**). Participants with diabetes had significantly higher prevalence of cognitive dysfunction in all three domains compared to persons without diabetes, and were 1.27 times (95%CI=1.11–1.46) more likely to have dysfunction in multiple domains compared to participants without diabetes (**Supplemental Figure 1**).

Among persons with diagnosed diabetes, those with the longest duration of diabetes (>15 years) had significantly higher cognitive dysfunction in all domains (**Figure 2**), than persons with shorter duration of diabetes. Participants with newly diagnosed diabetes (duration <5 years) had significantly more cognitive dysfunction in memory compared to persons without diabetes or with diabetes duration of 5-10 years. Associations remained significant even after full adjustment (**Supplemental Figure 2**).

Within each HbA1c category except prediabetes (HbA1c 5.6-6.4%), participants with glucose peaks had higher prevalence of cognitive dysfunction compared to participants without glucose peaks (**Figure 3**). For memory, the highest difference between 1,5-AG groups were among participants with HbA1c <5% (PR=1.93, p-value=0.079), HbA1c 5-5.6% (PR=1.27, p-value=0.028), and among persons with diabetes and HbA1c ≥7% (PR=1.31, p-value=0.108) (**Figure 3, Panel A**). Results were similar for executive function (**Figure 3, Panel B**).

Trends were similar across HbA1c categories when we examined continuous domain Z scores instead of dysfunction by diabetes status (**Supplemental Figure 3**) and when we defined impairment using expert reviewer classification of MCI/dementia (**Supplemental Figure 4**).

CONCLUSIONS

In this study of community-dwelling adults aged 67 to 90, we found that diabetes, diabetes duration, and glycemic peaks measured by 1,5 AG within narrow categories of HbA1c, was associated with cognitive dysfunction in memory, language, and executive function. We found the highest prevalence of cognitive dysfunction among participants without diagnosed diabetes and low-normal HbA1c (<5%), participants with diabetes, and those with longer duration of diagnosed diabetes, even after full adjustment. In fully adjusted models, participants with diabetes were 13%, 20%, and 11% more likely to have dysfunction in memory, language, and executive function, respectively, compared to participants without diabetes. Additionally, participants with diabetes were 27% more likely to have dysfunction in 2 or 3 domains, than those without diabetes. Finally, we found that within HbA1c categories, participants who had recent glucose peaks (1,5-AG <10 μg/mL) were more likely to have cognitive dysfunction compared to those without evidence of peaks.

Estimates of cognitive impairment have been reported in many populations[24], but few have reported diabetes- or HbA1c-specific estimates. A study of older adults in China reported a prevalence of MCI of 13.5% among persons with diabetes, although no information was provided by cognitive domains of glycemic control[25]. To our knowledge, ours is the first study to examine the relationship of cognitive function with subclinical hyperglycemic states defined by HbA1c and glucose control and glucose peaks in a community-based older population.

We found that persons with recent glucose peaks had higher prevalence of cognitive impairment across all HbA1c categories except prediabetes. Among persons in the normoglycemic group (no diabetes, HbA1c 5-5.6%), those with glucose peaks compared to those without peaks were 26%–27% more likely to have impairment in the memory and executive function domains. Similarly in participants with diagnosed diabetes and HbA1c≥7%, those with glucose peaks compared to those without were 31% and 41% more likely to have impairment in these two domains, respectively. Glucose peaks are very common among persons with diabetes,

even those with good glycemic control[9]. A study of more than 3200 participants with non-insulin-treated type 2 diabetes using in-home glucose readings over a 1-week period, found that 84% recorded at least one post-prandial blood glucose >160 mg/dL[9]. Additionally, among participants with HbA1c <7%, 38% had post-prandial glucose >160 mg/dL in more than 40% of the readings[9]. Glycemic variability may be related to microvascular and macrovascular complications in persons with diabetes[26], and may also have deleterious effects on cognitive function[27–29]. Fluctuating glucose levels have been shown to be more detrimental to neuronal cell functioning in vitro, compared to consistently high or low levels[30]. A few studies suggest that improving glycemic control benefits cognitive function[31–34], but sample sizes have been small.

Among persons without diagnosed diabetes, the group of participants with HbA1c <5% or HbA1c ≥6.5% had the highest estimated prevalence of cognitive impairment in executive function. It is important to note, however, that fewer than 4% of all participants were in these two groups. HbA1c value of <5% may be a marker of poor health. Prior research in ARIC[35,36] and in a nationally representative sample of adults (mean age 45 years)[37] has shown that persons with low HbA1c are at increased risk of death. Research among this interesting group of older adults with low HbA1c, and what value should be considered "low" in this population, may deserve further study.

We found similar estimates of cognitive impairment between the normoglycemic and prediabetes groups. Perhaps slight elevations in HbA1c beginning in late life do not carry similar risk of cognitive impairment as elevations occurring at an earlier age, particularly if this impairment is mediated through accumulation of vascular damage over time. In a prior study in ARIC, we found that participants with prediabetes in midlife had greater cognitive decline over 20 years compared to participants with no diabetes and HbA1c <5.7%[38]. Prospective research is needed to determine if similar patterns of cognitive decline emerge among older adults with hyperglycemia that develops in late life.

Current ADA guidelines do not include recommendations for screening for cognitive impairment among older adults with diabetes[8]. In our study, among persons with diabetes and an HbA1c ≥7%, we found a large prevalence of cognitive dysfunction in memory (25%) and executive function (34%), the domains most relevant for the management of diabetes. More research may be needed to determine whether subtle impairments in these domains, perhaps not readily apparent in clinical practice, affect diabetes self-management and whether screening for impairment in these domains among persons with diabetes would provide clinicians with useful information about appropriate medications or patient-specific glycemic targets, as recommended by the ADA.

Our study has a number of strengths. First, we examined a large, community-based cohort, allowing us to examine the prevalence of cognitive impairment across specific subgroups and exposures. Second, we used age-, education-, and race-adjusted normative data, which was developed in a group of ARIC participants who were free of both clinical and subclinical neurological disease[21]. Lastly, we used a battery of eight neuropsychological tests to represent three cognitive domains, which may better characterize impairment than using a simple cognitive screening test like the MMSE, as some previous studies have done.

Our study has a few limitations that should be considered. First, we had few participants in the low-normal HbA1c group and the undiagnosed diabetes group, making estimates in these groups less precise. Second, since our study is cross-sectional, we cannot establish the temporal relationships between glycemia and cognitive function. Lastly, selection bias is of great concern in any study of older adults. Participants with long-standing diabetes, or whose diabetes is not well controlled, and those with cognitive impairment (who are also more likely to have diabetes) are more likely to have died or be missing from our study. Indeed, the prevalence of MCI and dementia in the entire ARIC cohort, including those not examined at the 2011-2013 visit, has been estimated as nearly 30%[39]. As a result, our estimates of associations between cognitive

impairment and glycemic states may be biased toward the null, as surviving participants who attended the study visit may be more robust or in better health than participants who did not.

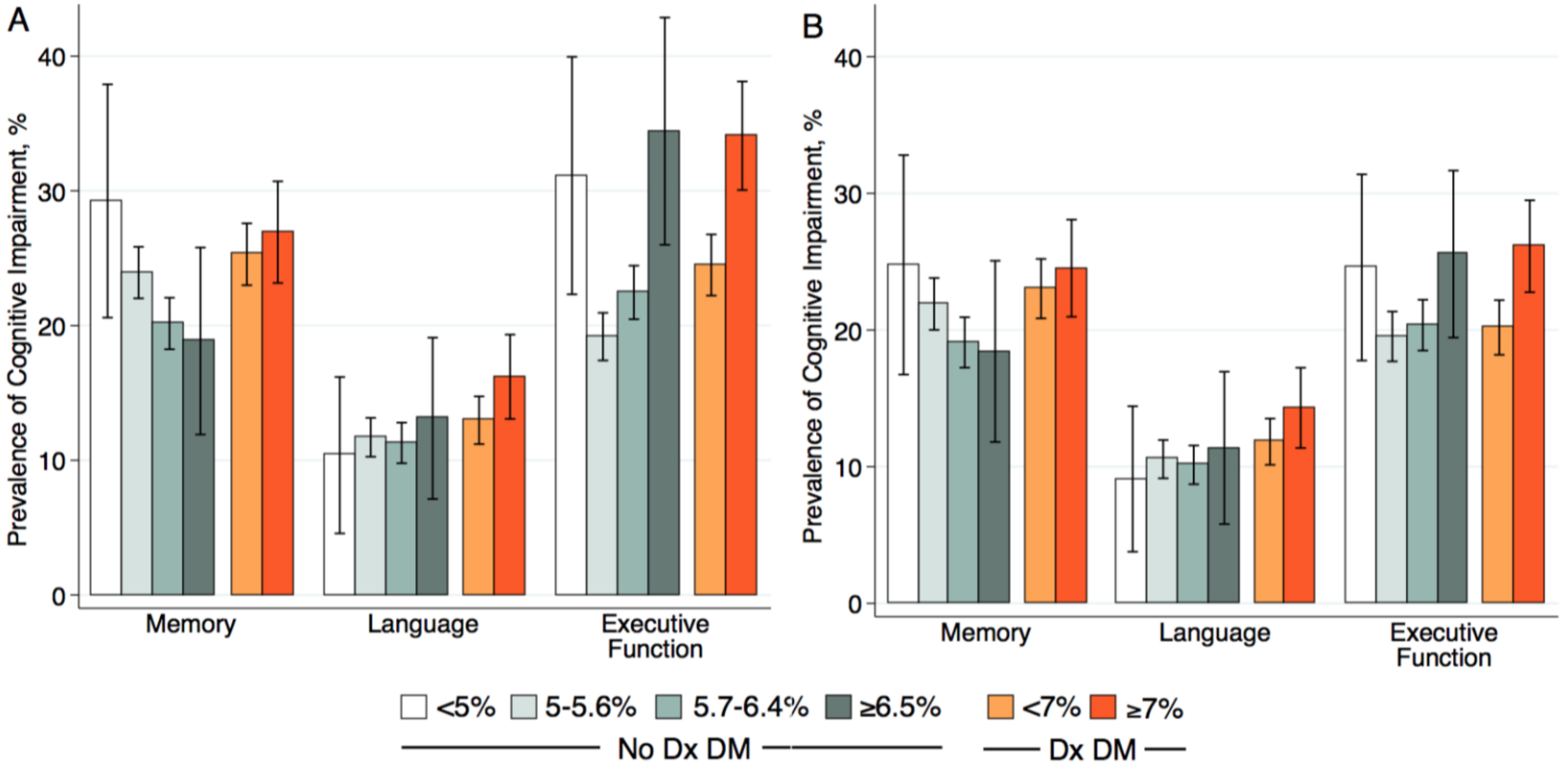
In summary, these results document important associations of specific cognitive impairments with diabetes, its duration, and aspects of glycemic control in older adults with diabetes. More research is needed to determine if these impairments interfere with diabetes self-management, to explore the association of cognitive impairments with low-normal HbA1c, to determine if targeting glucose peaks can improve cognitive function in older adults with diabetes, and lastly to determine if screening for cognitive impairment may allow for more targeted approach toward diabetes management.

Table 1. Study population characteristics by diabetes status and HbA1c category, the Atherosclerosis Risk in Communities Study, 2011-2013 (Visit 5), N=5,746

	No Diagnosed Diabetes				Diagnosed Diabetes	
	Low-Normal HbA1c <5%	Normo-glycemic HbA1c 5-5.6%	Pre-diabetes HbA1c 5.7-6.4%	Un-diagnosed HbA1c ≥6.5%	HbA1c <7%	HbA1c ≥7%
N (%)	106	1,914	1,692	122	1,381	531
Age, years	74.8 (5.1)	75.3 (5.0)	75.7 (5.2)	76.5 (5.3)	75.7 (5.2)	75.0 (5.0)
Female, %	43.4	59.9	61.0	64.8	58.4	55.2
Black, %	31.1	10.8	21.7	44.3	24.4	35.8
HbA1c, %	4.7 (0.3)	5.4 (0.2)	5.9 (0.2)	6.8 (0.3)	6.0 (0.5)	8.0 (1.1)
1,5-AG, μg/mL	16.9 (6.6)	16.7 (6.0)	17.0 (6.0)	16.3 (6.1)	15.6 (6.2)	8.6 (6.0)
1,5-AG <10 μg/mL, %	14.2	13.0	11.9	14.0	19.7	65.4
Diabetes duration, years	-	-	-	-	9.1 (6.1)	13.5 (6.5)
Diabetes meds, %						
Biguanides	0.0	0.1	0.1	0.0	30.9	53.1
Sulfonylureas	0.0	0.0	0.0	0.0	15.8	39.7
Insulin	0.0	0.0	0.0	0.0	6.4	36.0
DPP-4 inhibitors	0.0	0.0	0.0	0.0	4.6	10.7
TZDs	0.0	0.0	0.0	0.0	3.9	5.1
Education, %						
<HS	11.3	8.1	11.6	18.0	17.3	19.0
HS	37.7	40.2	43.0	41.0	43.6	44.3
>HS	50.9	51.7	45.4	41.0	39.1	36.7
BMI, kg/m^2	27.4 (5.7)	27.2 (4.9)	28.4 (5.4)	30.5 (6.1)	30.2 (5.8)	31.9 (6.2)
Hypertension, %	72.1	64.5	71.9	86.7	83.2	89.3
History of CHD, %	16.0	9.4	14.2	14.8	18.5	19.0
History of stroke, %	6.6	2.0	2.8	4.9	4.3	5.7
Total cholesterol, mg/dL	183 (37)	191 (29)	186 (35)	182 (36)	169 (39)	170 (39)
HDL-C, mg/dL	54 (25)	56 (14)	53 (17)	49 (22)	49 (20)	45 (23)
LDL-C, mg/dL	105 (42)	111 (41)	108 (41)	107 (40)	94 (40)	93 (42)
Triglycerides*, mg/dL	105 (65)	104 (60)	112 (60)	115 (66)	113 (70)	143 (95)
Current smoker, %	4.7	5.2	6.1	8.2	5.7	4.5
Current drinker, %	49.1	57.1	49.3	41.0	40.4	32.6
Apolipoprotein E4 alleles						
0	57.4	72.1	72.6	64.2	73.2	72.0
1	40.6	26.1	25.4	33.3	24.5	26.3
2	2.0	1.8	1.9	2.5	2.3	1.8
Depressive symptoms†, %	4.7	4.7	6.3	12.3	10.5	11.8
Cognitive Scores						
Memory	-0.14 (1.12)	0.09 (1.01)	0.04 (0.98)	-0.17 (0.97)	-0.07 (0.99)	-0.20 (1.00)
Executive function	-0.16 (1.13)	0.23 (0.93)	0.02 (0.99)	-0.40 (1.03)	-0.13 (0.99)	-0.43 (1.04)
Language	-0.13 (1.07)	0.20 (0.93)	0.04 (1.00)	-0.45 (1.00)	-0.14 (1.01)	-0.35 (1.02)

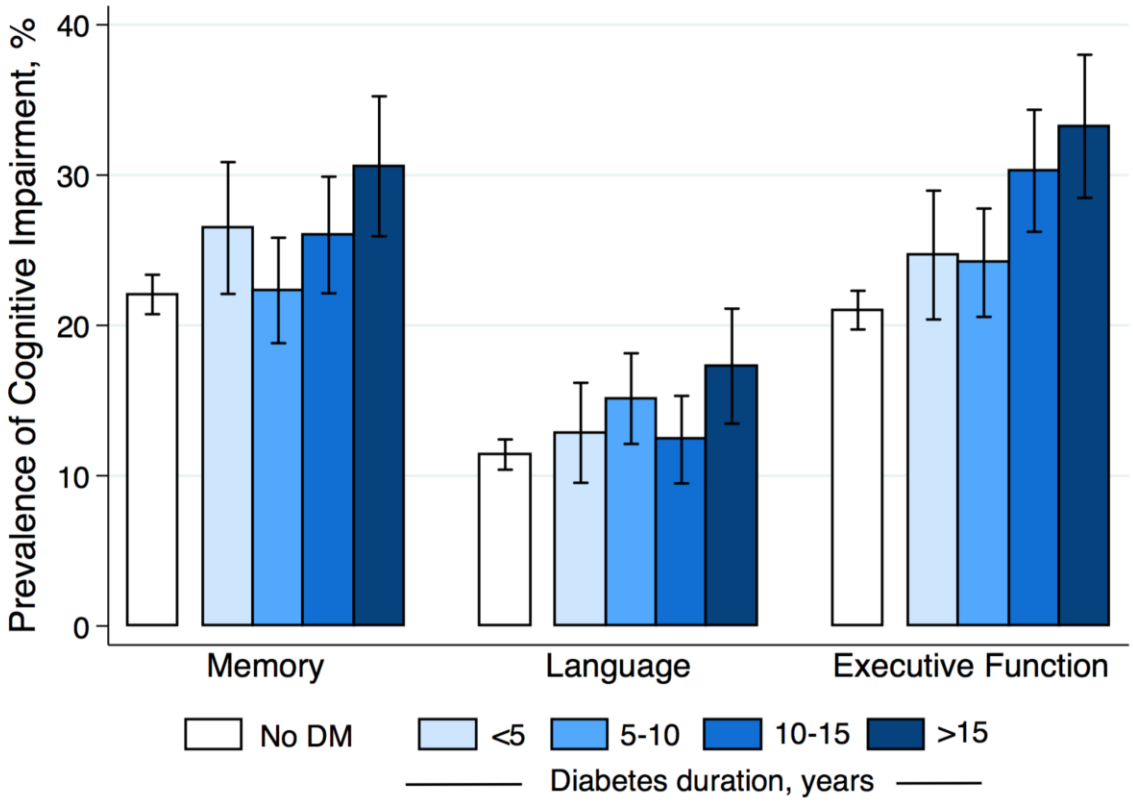
Values shown as mean (SD) or %. * reported as median (interquartile range)
† Defined as a score ≥9 on the 11-item Center for Epidemiologic Studies Depression Scale (CESD-11)
Diabetes was based on self-reported physician diagnosis, diabetes medication use, or HbA1c ≥6.5%.
Abbreviations: HbA1c, hemoglobin A1c; DPP-4, dipeptidyl peptidase-4; TZD, thiazolidinediones; meds, medications; HS, high school; BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;

Figure 1. Unadjusted and adjusted prevalence of cognitive dysfunction by diagnosed diabetes status and HbA1c category



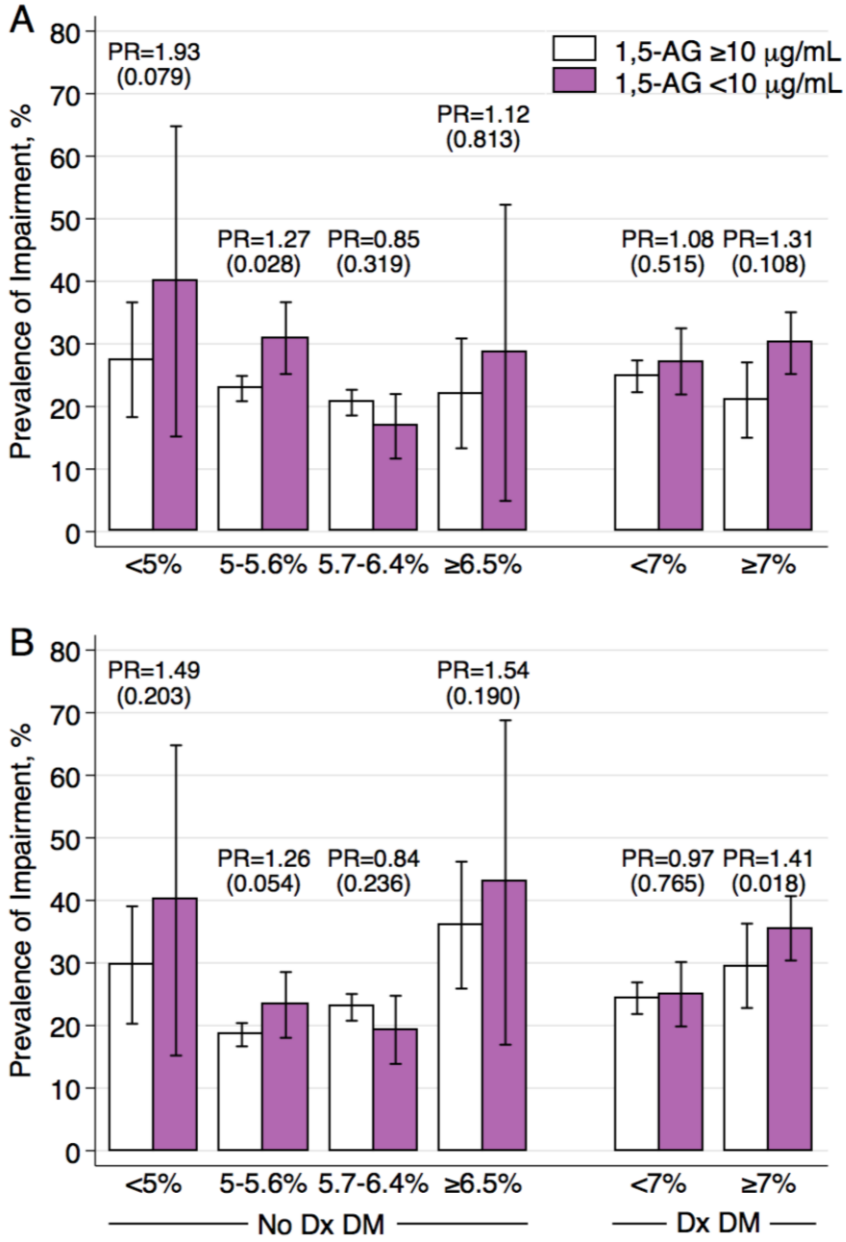
Legend: Diagnosed diabetes ("Dx DM") was based on self-reported physician diagnosis or diabetes medication use. Cognitive impairment in each domain was defined as test scores more than 1.5 standard deviations below age-, race-, and education-adjusted norms among 2 or more tests in a given domain.
Panel A: unadjusted prevalence estimates
Panel B: Prevalence values are estimated from Poisson regression models, adjusted for age, race, sex, education, hypertension, history of coronary heart disease, history of stroke, drinking status, cigarette smoking status, and APOE e4

Figure 2. Prevalence of cognitive dysfunction by domain and diabetes duration



Legend: Prevalence estimates are shown unadjusted. Diabetes was based on self-reported physician diagnosis or diabetes medication use, and duration was calculated using the date a participant first reported a diagnosis or medication use (during a previous visit or during the annual follow-up telephone call). Cognitive impairment in each domain was defined as test scores more than 1.5 standard deviations below age-, race-, and education-adjusted norms among 2 or more tests in a give domain. The "No DM" (no diabetes) group included participants without a self-reported diagnosis of diabetes, who were not taking glucose-lowering medication, and who had an HbA1c of 5-6.4% (participants with undiagnosed diabetes were excluded).

Figure 3. Prevalence of cognitive dysfunction in memory and executive function by diagnosed diabetes status, HbA1c, and 1,5-anhydroglucitol (1,5-AG)



Legend: Prevalence estimates of cognitive impairment are shown unadjusted. Prevalence ratios (PRs) are estimated from Poisson regression models, adjusted for age, race, sex, education, hypertension, history of coronary heart disease, history of stroke, drinking status, cigarette smoking status, APOE e4, and hemoglobin A1c. Diagnosed diabetes (Dx DM) was based on self-reported physician diagnosis or diabetes medication use. Cognitive impairment in each domain was defined as test scores more than 1.5 standard deviations below age-, race-, and education-adjusted norms among 2 or more tests in a given domain.
Panel A: memory domain
Panel B: executive function domain

Conclusion

This dissertation examined the associations between diabetes and measures of glycemia with cognitive function and dementia. We examined the association between diabetes, mean glycemia (measured using HbA1c), and glycemic peaks (measured using 1,5-anhydroglucitol) with 20-year cognitive decline and incident dementia. We also examined the association between diabetes, glycemia, and cognitive impairment in older adults. Finally, we addressed two methodological issues, including handling missing cognitive data in longitudinal analyses of change in cognitive function (Chapter 2), and characterizing the factor structure of the ARIC-NCS neurocognitive battery (Chapter 4), the results of which were applied in longitudinal analyses (Chapters 3) and cross-sectional analyses of ARIC-NCS data (Chapter 5), respectively.

Summary of findings

In Chapter 1 we examined the association between diabetes, levels of HbA1c, and cognitive decline over 20 years[1]. We found that participants with diabetes and prediabetes had greater cognitive decline over the subsequent two decades. We estimated that the additional decline in cognitive test scores among persons with diabetes was equivalent to being approximately 5 years older at baseline (ie differences in mean cognitive test scores of a 55 year old without diabetes compared to a 60 year old without diabetes). This "accelerated aging" among persons with diabetes offers an important avenue for prevention, as delaying the onset of dementia by even a couple of years, at the population level, could reduce the prevalence of dementia by more than 20% over the next 30 years[2]. We also found that among persons with diabetes, those with HbA1c $\geq$7% (a typical definition for poorly controlled diabetes) had greater decline during the same period than persons with diabetes who had HbA1c values <7%. These data suggest that primary prevention of diabetes or glucose control in midlife may protect against later-life cognitive decline.

In Chapter 2 we explored the bias that arises in longitudinal studies of cognitive function, as participants who have diabetes and experience cognitive deficits are less likely to attend study visits. We used multiple imputation by chained equations (MICE) to impute cognitive performance scores of participants who did not attend the 2011-2013 follow-up exam of the ARIC study. Using observed and simulated data we found that MICE produced unbiased imputations of cognitive function. Simulations showed a substantial reduction in the bias of the 20-year association between diabetes and cognitive decline comparing MICE (3% bias) to analysis of available data only (23% bias). Finally, associations between diabetes and 20-year cognitive decline were substantially stronger with MICE than in the analyses without imputed values. Multiple imputation is commonly used in the statistical literature, but has not been widely applied in epidemiologic studies. Large cohort studies often collect auxiliary information outside of study visits, and multiple imputation may be ideally suited for these situations, where there is some information available on some participants at some time points (ie not all participants have the same data, but there is overlap in the data between persons who do and those who do not attend study visits). Our results suggest that when such data are available for participants who do not attend study visits, MICE is an effective tool for imputing cognitive performance as the outcome, and may improve assessment of cognitive decline.

Building on the work in Chapter 1 and using the imputation methods developed in Chapter 2, in Chapter 3 we examined the association between levels of 1,5-anhydroglucitol (a measure of glycemic peaks) and cognitive decline over 20 years and dementia. In fully adjusted models, we found that among persons with diabetes and HbA1c <7%, those with glucose peaks had higher risk of dementia compared to persons in the same group but without peaks, though the results were not statistically significant (HR=1.31, p-value =0.32). We found that among persons with diabetes and HbA1c ≥7%, those with glucose peaks had a statistically significant higher risk of dementia compared to persons in the same group but without peaks (HR=1.76, p-value =0.04). For analyses examining 20-year cognitive decline, we found that the association between diabetes

and cognitive decline seemed to be modified by glucose peaks. That is, persons with glucose peaks had the most cognitive decline compared to persons without peaks. A few studies using continuous glucose monitors have found associations between measures of glycemic variability and cognitive impairment and brain atrophy, independent of both mean levels of glycemia and hypoglycemic episodes[29–31], but long-term prospective studies have not been conducted. Our study, including over 20 years of follow-up, suggests that glycemic instability, reflected by glucose peaks, particularly in persons with HbA1c ≥7%, may be an important contributor to vascular damage to the brain. This study also adds to the literature on the clinical utility of 1,5-AG and the debate on the utility of glycemic variability[3].

In Chapter 4 we examined the factor structure of the cognitive battery given to participants at the ARIC Neurocognitive study (ARIC-NCS) visit (2011-2013). We found that the cognitive battery of 11 tests represented 3 underlying constructs of memory, language, and sustained attention and processing speed. Additionally, we found that these constructs were not different (invariant) by age, race, sex, education, diabetes, and hypertension, providing compelling evidence for the robustness of cognitive domains measured by the test battery across demographic and vascular factors. Establishing invariance by vascular risk factors is particularly important, as diabetes and hypertension are common. Establishing invariance for these very common vascular risk factors in a diverse sample is a vital prerequisite for investigations into the contributions of vascular predictors (such as hypertension and diabetes) to cognition in older adults. To our knowledge, this is the first study to report invariance by vascular risk factors. These findings are assuring that one can use the same cognitive domain constructs to pursue questions regarding the vascular contribution to cognitive impairment.

In Chapter 5 we characterized the level of cognitive impairment by diabetes status and levels of glycemia, across domains developed in Chapter 4. Estimates of cognitive impairment have been reported in many populations[24], but few have reported diabetes- or HbA1c-specific estimates, or examined associations with glycemic peaks. Using age-, race-, and education-

adjusted norms, we found that persons with diabetes had higher levels of cognitive dysfunction. Additionally, we found the largest prevalence of cognitive impairment among participants with longer duration of diabetes, with diabetes and HbA1c ≥7%, with no diabetes and HbA1c <5%, and among persons with glucose peaks. These results document important associations of specific cognitive impairments with diabetes, its duration, and aspects of glycemic control in older adults with diabetes and have implications for guidelines and future research (described below).

Public health significance and implications

The U.S. population is rapidly aging, with the number of persons 65 and older expected to reach more than 70 million by 2030[4]. An estimated 13.9% of older adults have dementia[5], and another 22% have cognitive impairment without dementia[6]. Dementia carries tremendous burden at the individual, caregiver, and health care levels. On average, persons with Alzheimer's Disease, the most common type of dementia, live 4-8 years after their diagnosis[7–10]. Additionally, most of this time is spent in the more severe stages of the disease[11], often in nursing homes, resulting in loss of independence and quality life years. Family members provide the vast majority of unpaid help to care for persons with dementia, leading to physical and emotional stress for these caregivers. Furthermore, in 2014, caregivers provided an estimated 17.9 billion hours of unpaid care to persons with dementia, representing nearly $218 billion[12]. Lastly, the total cost of care for persons with dementia in 2015 was estimated to be $226 billion, including $44 billion out-of-pocket costs, and $153 billion from Medicare and Medicaid[12].

The burden of dementia is compounded by the fact that currently only a handful of treatment options exist, and none stop or reverse the course of AD or most other dementias[12]. As a result, there is tremendous interest in prevention via modifiable risk factors. In its report of the summary of evidence for modifiable risk factors[13], the Alzheimer's Association stated that "on balance, the association between diabetes and dementia appears strong, but not conclusive" (p. 719), however they nevertheless concluded that there is moderate evidence that diabetes increases

the risk of dementia, and strong evidence that it increases the risk of cognitive decline. While the evidence for diabetes as a risk factor for cognitive decline and dementia is becoming clearer, more research is needed to tease out the underlying pathophysiological mechanisms that link diabetes to cognitive decline. Identifying the aspects of diabetes that may be particularly detrimental to cognitive function may provide important treatment targets and lead to the prevention of cognitive decline.

The prevalence of type 2 diabetes has increased substantially in the past few decades, currently affecting approximately 10% of adults age 20 and older[14,15]. Diabetes also disproportionally affects older adults: among adults age 65 and older, the prevalence of diabetes and prediabetes is 22% and 24%, respectively[14]. The number of adults with both diabetes and cognitive impairment is growing, and represents challenges for patient care, as domains typically associated with diabetes may also be most relevant for its management. Perhaps more importantly, delaying or preventing diabetes, in addition to reducing the micro- and macrovascular complications associated with the disease, may also prevent cognitive decline and delay progression to dementia.

Glycemic peaks are common in older adults. A study of more than 3200 participants with non-insulin-treated type 2 diabetes using in-home glucose readings over a 1-week period, found that 84% of participants recorded at least one post-prandial blood glucose >160 mg/dL[16]. Even among persons with well controlled diabetes (HbA1c <7%), 38% had post-prandial glucose >160 mg/dL in more than 40% of the readings[16]. Glycemic variability may be related to microvascular and macrovascular complications in persons with diabetes[17], and may also have deleterious effects on cognitive function[18–20]. Additionally, fluctuating glucose levels have been shown to be more detrimental to neuronal cell functioning in vitro, compared to consistently high or low levels[21].

Given the trends in diabetes and the aging of the U.S. population, identifying modifiable risk factors and treatment targets for the prevention of cognitive decline and dementia has the

potential to have tremendous impact at the population level, in addition to the reducing the burden for individuals. Brookmeyer et al estimated that at the population level, delaying the onset of AD by even a couple of years could reduce its prevalence by more than 20% over the next 30 years[2].

Lastly, our finding that cognitive impairment is common among older adults with diabetes in two domains relevant for the management of diabetes (~20-30% impairment in memory and executive function) has implications for screening for cognitive impairment in this group. In the 2016 Standards of Medical Care in Diabetes section on older adults, the ADA recommends that clinicians "consider the assessment of medical, functional, mental, and social geriatric domains for diabetes management in older adults to provide a framework to determine targets and therapeutic approaches" and that "screening for geriatric syndromes may be appropriate in older adults experiencing limitations in their basic and instrumental activities of daily living, as they may affect diabetes self-management" (p. S81)[22]. Both of the recommendations are based on evidence from "expert consensus or clinical experience" (p. S2)[22], however the ADA does not explicitly recommend screening for cognitive impairment in older adults with diabetes. Given the relatively high prevalence of cognitive impairment reported in this dissertation, and that impairment may not be readily apparent in clinical practice (persons in our study were healthy enough to attend study visits), screening for cognitive impairment in older adults with diabetes may help "clinicians to help their patients reach individualized glycemic, blood pressure, and lipid targets" (p. S82)[22] as recommended by the ADA. More research is needed to quantify the potential costs and benefits of this screening.

Future directions

More research is needed on several fronts. First, additional studies are needed to determine if targeting glucose peaks, in addition to average glucose, among persons with diabetes can reduce the risk of dementia and cognitive decline, or reduce the prevalence of cognitive impairment among older adults. A few studies suggest that improving glycemic control has

benefits on cognitive function[23–25], but sample sizes have been small, and most have focused on mean glycemia.

To date, there has been one randomized controlled trial (RCT) that specifically examined the effects of targeting postprandial glucose excursions on cognitive function[26]. In this trial, approximately 150 participants with type 2 diabetes (mean age 74, 51% female) were randomized to repaglinide, an oral prandial glucose regulator, or glibenclamide, a sulfonylurea, and followed at three-month intervals for one year. After randomization, the two groups showed similar declines in both HbA1c and fasting plasma glucose (FPG) over one year (there was no significant differences in HbA1c between the two groups during follow-up). However, the group treated with repaglinide showed significantly greater decline in the coefficient of variation of FPG, which was estimated using data from self-monitoring blood glucose done by participants during the two weeks preceding each follow-up visit. Cognitive function was measured using the Mini-Mental State Examination (MMSE) and using a battery of neuropsychological tests, including the Trail Making Test (parts A and B), the Digit Span test (forward and backward), and the Word Fluency Test, which were summarized using a global composite. The group of participants randomized to glibenclamide showed a small but statistically significant decline in both MMSE and the global composite, while the group randomized to repaglinide showed no decline during the year of follow-up.

This study adds support to the findings and implications of this dissertation that targeting glycemic peaks may be beneficial for cognitive function. It is important to note that this RCT was conducted in participants age 60-78 and had only one year of follow-up. Previous studies have shown weaker associations when risk factors are measured in late life compared to midlife[27–29], and thus interventions in late life may be less beneficial compared to interventions in midlife. As a result, an RCT targeting postprandial excursions in midlife may be worthwhile, however the duration of follow-up needed to observe significant cognitive decline at this age may make an RCT infeasible. Nevertheless, such a study might use intermediate measures, such as MRI

measures, which may show subtle changes in brain structure. Such changes may not manifest in lower neuropsychological test scores over a short time period, but may be a surrogate for long-term decline. ARIC may be suitable to study changes in brain volume among persons with glycemic peaks using MRI data collected at visits 3 (1993-1995), the Brain MRI visit (2004-2006), and 5 (2011-2013).

Second, our analysis of cognitive impairment in older adults (Chapter 5) raises several avenues for future research, including determining if the level of impairment found in this dissertation (~20-30%) interferes with one's ability to self-manage their diabetes, determining if screening for cognitive impairment in older adults with diabetes can improve outcomes, and further exploring the association between low-normal HbA1c (<5%) in older adults without diabetes and cognitive function. Previous studies have found increased risk of death among persons with low HbA1c[30–32], but few studies have examined characteristics of this unique group of individuals, especially in relation to cognitive function. While our results add to the evidence suggesting that low HbA1c may be a marker of poor health, more research is needed to clarify associations and clinical implications.

Third, we explored two aspects of glycemia in this dissertation. Examining other biomarkers of glycemia, such as fructosamine[33] or glycated albumin[34,35], which reflect average glycemia over 1-3 weeks, and potentially other determinants of glycemia such as insulin or insulin resistance, maybe provide additional information about glycemic variability and provide insight into the pathophysiological mechanisms that link diabetes and cognitive function. Examining additional biomarkers raises the methodological issue about how best to incorporate information across multiple markers. One potential approach may be the use of latent profile analysis, which aims to create classes, or groups, of individuals based on measurement of continuous variables (such as biomarkers). Identifying the number of classes of individuals could be important for several reasons. First, it may provide a good summary measure of information from many markers. Second, identifying individual classes may give us insight into the unique

information provided by each marker, and may identify individuals most (or least) at risk for cognitive decline or other outcomes. This line of research mayb be beneficial to other fields where multiple biomarkers are used in the diagnosis or management of disease.

Limitations

There are several limitations to this dissertation. First, this dissertation examined the association between cognitive function and HbA1c and 1,5-AG, two aspects of glycemia. We did not have rigorous measurement of other aspects of glycemia including short- or long-term glycemic variability or hypoglycemia, or measures of insulin resistance or insulin sensitivity, which have been linked to cognitive function[19,20,36,37]. Second, the studies included in this dissertation are observational, so we cannot definitively establish causal relationships between glycemia and cognitive function.

Strengths

There are several strengths to this dissertation. First, the long duration of the ARIC study allowed us to estimate associations between diabetes and cognitive function over 20 years. A review by Cukierman and colleagues[38] published in 2005 included only one study with a mean follow-up of more than 6 years, and since 2005 only a handful of studies reported declines over 10 year[39–42]. Additionally, only one study reported associations with diabetes diagnosed before age 65, which is important as associations between risk factors and cognitive decline appear weaker when risk factors are measured in late life compared to midlife[27–29]. Second, we used validated neuropsychological tests as measures of cognitive function, and community surveillance and retrospective dementia ascertainment allowed us to examine associations with incident dementia. Lastly to our knowledge this is one of the first studies to examine prospective associations between glucose peaks and cognitive function and dementia.

Summary

In conclusion, we have documented the association of diabetes, mean glycemia (HbA1c), and glucose peaks (1,5-AG) with cognitive decline and dementia. This dissertation adds to the literature that diabetes is a risk factor for cognitive decline and dementia and that prevention of diabetes or glycemic control in midlife may prevent or delay cognitive decline. To our knowledge, no studies to date have examined the prospective association between glucose peaks and cognitive decline and dementia, leading to future avenues of research regarding potential treatment targets. This dissertation addresses several gaps in the literature of this area, in that our studies were prospective, had long duration of follow-up (~20 years), and we were able to well-characterize diabetes using HbA1c, 1,5-AG, and other rigorously obtained information in the ARIC Study. Additionally, we have documented the utility of multiple imputation, which is rarely used in epidemiologic studies, to impute cognitive function as the outcome, and we showed that biases in associations of interest are reduced as a result. Lastly, we have documented invariance of ARIC-NCS cognitive test battery across vascular risk factors, which to our knowledge have not been previously shown in the literature, but which is vital to establish to answer research questions regarding the vascular contributions to cognitive impairment.

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APPENDIX A: Supplemental material for Chapter 1

Supplemental Table 1: Average difference in 20-year decline in global Z score, delayed word recall, digit symbol substitution, and word fluency among persons with a history of diagnosed diabetes compared to persons without diabetes, white race

No attrition adjustment

Test	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference* Estimate (95% CI)	Percent†
Global Z	**-0.81 (-0.84, -0.78)**	**-0.96 (-1.04, -0.87)**	**-0.15 (-0.24, -0.07)**	19%
DWRT	**-0.97 (-1.02, -0.92)**	**-1.11 (-1.25, -0.97)**	**-0.14 (-0.28, -0.00)**	14%
DSST	**-0.78 (-0.80, -0.765**	**-0.87 (-0.94, -0.81)**	**-0.10 (-0.16, -0.04)**	13%
WFT	**-0.15 (-0.18, -0.13)**	**-0.26 (-0.34, -0.18)**	**-0.10 (-0.18, -0.03)**	67%

Attrition-adjusted

	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference* Estimate (95% CI)	Percent†
Global Z	**-0.81 (-0.85, -0.77)**	**-1.09 (-1.20, -0.97)**	**-0.27 (-0.39, -0.16)**	34%
DWRT	**-0.99 (-1.05, -0.93)**	**-1.19 (-1.34, -1.03)**	**-0.20 (-0.35, -0.04)**	20%
DSST	**-0.78 (-0.80, -0.75)**	**-0.94 (-1.02, -0.85)**	**-0.16 (-0.25, -0.08)**	21%
WFT	**-0.15 (-0.18, -0.12)**	**-0.39 (-0.53, -0.25)**	**-0.24 (-0.39, -0.09)**	158%

* Calculated as the difference in 20-year decline between persons without and with diabetes (negative values indicate greater decline in persons with diabetes)

† Calculated as the difference expressed as a percentage of the decline in those without diabetes. That is, (decline in participants without diabetes – decline in participants with diabetes)/(decline in participants without diabetes); thus a value of 20% indicates a 20% greater decline in those with diagnosed diabetes compared to those without.

Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=23,287 total records, with N=10,189 participants at visit 2(N=977 with diabetes), N=8,431 at visit 4(N=711 with diabetes), and N=4,667 at visit 5(N=240 with diabetes).

Supplemental Table 2: Average difference in 20-year decline in global Z score, delayed word recall, digit symbol substitution, and word fluency among persons with a history of diagnosed diabetes compared to persons without diabetes, black race

No attrition adjustment

Test	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference* Estimate (95% CI)	Percent†
Global Z	**-0.78 (-0.89, -0.67)**	**-0.93 (-1.09, -0.77)**	**-0.15 (-0.27, -0.03)**	19%
DWRT	**-0.93 (-1.14, -0.72)**	**-0.86 (-1.13, -0.60)**	0.06 (-0.12, 0.24)	-7%
DSST	**-0.62 (-0.69, -0.55)**	**-0.81 (-0.91, -0.71)**	**-0.19 (-0.26, -0.11)**	30%
WFT	**-0.27 (-0.36, -0.18)**	**-0.40 (-0.53, -0.27)**	**-0.13 (-0.22, -0.03)**	48%

Attrition-adjusted

	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference* Estimate (95% CI)	Percent†
Global Z	**-0.82 (-0.95, -0.70)**	**-0.99 (-1.17, -0.81)**	**-0.17 (-0.30, -0.03)**	20%
DWRT	**-0.98 (-1.21, -0.75)**	**-0.91 (-1.21, -0.61)**	0.07 (-0.14, 0.29)	-7%
DSST	**-0.63 (-0.71, -0.55)**	**-0.83 (-0.95, -0.72)**	**-0.20 (-0.30, -0.11)**	32%
WFT	**-0.28 (-0.38, -0.18)**	**-0.43 (-0.58, -0.29)**	**-0.15 (-0.27, -0.04)**	55%

* Calculated as the difference in 20-year decline between persons without and with diabetes (negative values indicate greater decline in persons with diabetes)

† Calculated as the difference expressed as a percentage of the decline in those without diabetes. That is, (decline in participants without diabetes – decline in participants with diabetes)/(decline in participants without diabetes); thus a value of 20% indicates a 20% greater decline in those with diagnosed diabetes compared to those without.

Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=6,771 total records, with N=3,162 participants at visit 2(N=802 with diabetes), N=2,289 at visit 4(N=498 with diabetes), and N=1,320 at visit 5(N=206 with diabetes).

Supplemental Table 3: Average difference in 14-year decline in global Z score, delayed word recall, digit symbol substitution, and word fluency among persons with prevalent diagnosed diabetes at visit 2 or incident diagnosed diabetes or visit 4, compared to persons without diabetes at either visit, white race

		No attrition adjustment		Attrition adjusted	
Test	Diabetes duration (years)	Absolute 14-year decline Estimate (95% CI)	Difference* Estimate (95% CI)	Absolute 14-year decline Estimate (95% CI)	Difference* Estimate (95% CI)
Global Z	No diabetes	**-0.72 (-0.75, -0.69)**	(reference)	**-0.72 (-0.76, -0.69)**	(reference)
	< 3	**-0.90 (-1.00, -0.79)**	**-0.18 (-0.28, -0.07)**	**-0.91 (-1.02, -0.79)**	**-0.18 (-0.30, -0.07)**
	3 - 6	**-0.87 (-0.99, -0.75)**	**-0.15 (-0.27, -0.03)**	**-0.89 (-1.01, -0.76)**	**-0.16 (-0.29, -0.04)**
	6 - 9	**-0.82 (-0.98, -0.66)**	-0.10 (-0.26, 0.06)	**-0.91 (-1.14, -0.69)**	-0.19 (-0.42, 0.04)
	> 9	**-0.87 (-0.97, -0.77)**	**-0.15 (-0.25, -0.05)**	**-0.93 (-1.05, -0.82)**	**-0.21 (-0.32, -0.09)**
	p-value-for-trend	**0.007**	-	**0.006**	-
DWRT	No diabetes	**-0.92 (-0.97, -0.87)**	(reference)	**-0.92 (-0.98, -0.87)**	(reference)
	< 3	**-1.07 (-1.22, -0.91)**	-0.15 (-0.31, 0.01)	**-1.08 (-1.25, -0.91)**	-0.16 (-0.33, 0.01)
	3 - 6	**-1.10 (-1.28, -0.92)**	**-0.18 (-0.36, -0.01)**	**-1.15 (-1.33, -0.96)**	**-0.22 (-0.41, -0.04)**
	6 - 9	**-1.05 (-1.29, -0.82)**	-0.13 (-0.37, 0.10)	**-1.11 (-1.36, -0.87)**	-0.19 (-0.43, 0.05)
	> 9	**-1.05 (-1.21, -0.89)**	-0.13 (-0.29, 0.03)	**-1.11 (-1.28, -0.93)**	**-0.18 (-0.36, -0.01)**
	p-value-for-trend	**0.011**	-	**0.010**	-
DSST	No diabetes	**-0.65 (-0.68, -0.63)**	(reference)	**-0.66 (-0.69, -0.63)**	(reference)
	< 3	**-0.78 (-0.86, -0.70)**	**-0.13 (-0.21, -0.05)**	**-0.78 (-0.86, -0.70)**	**-0.12 (-0.20, -0.04)**
	3 - 6	**-0.73 (-0.82, -0.64)**	-0.08 (-0.16, 0.01)	**-0.73 (-0.81, -0.64)**	-0.07 (-0.15, 0.02)
	6 - 9	**-0.68 (-0.81, -0.54)**	-0.02 (-0.16, 0.11)	**-0.71 (-0.84, -0.58)**	-0.05 (-0.18, 0.08)
	> 9	**-0.82 (-0.90, -0.73)**	**-0.16 (-0.25, -0.07)**	**-0.87 (-0.98, -0.77)**	**-0.21 (-0.32, -0.11)**
	p-value-for-trend	**0.002**	-	**<0.001**	-
WFT	No diabetes	**-0.11 (-0.14, -0.08)**	(reference)	**-0.11 (-0.14, -0.08)**	(reference)
	< 3	**-0.21 (-0.30, -0.12)**	**-0.10 (-0.19, -0.01)**	**-0.21 (-0.31, -0.12)**	**-0.10 (-0.19, -0.01)**
	3 - 6	**-0.20 (-0.32, -0.09)**	-0.09 (-0.21, 0.03)	**-0.18 (-0.32, -0.05)**	-0.07 (-0.21, 0.07)
	6 - 9	**-0.21 (-0.35, -0.06)**	-0.10 (-0.24, 0.05)	**-0.33 (-0.62, -0.04)**	-0.22 (-0.51, 0.08)
	> 9	**-0.19 (-0.28, -0.09)**	-0.07 (-0.17, 0.02)	**-0.24 (-0.35, -0.13)**	**-0.12 (-0.23, -0.02)**
	p-value-for-trend	**0.006**	-	**0.006**	-

* Calculated as the difference in 14-year decline between persons with no diabetes at either visit and persons who have prevalent diabetes at visit 2 or develop diabetes between visits 2 and 4 (negative values indicate greater decline in those with prevalent or incident diabetes)

Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=13,098 total records, with N=8,431 at visit 4(N=711 with diabetes), and N=4,667 at visit 5(N=240 with diabetes)

Supplemental Table 4: Average difference in 14-year decline in global Z score, delayed word recall, digit symbol substitution, and word fluency among persons with prevalent diagnosed diabetes at visit 2 or incident diagnosed diabetes or visit 4, compared to persons without diabetes at either visit, black race

		No attrition adjustment		Attrition adjusted	
Test	Diabetes duration (years)	Absolute 14-year decline Estimate (95% CI)	Difference* Estimate (95% CI)	Absolute 14-year decline Estimate (95% CI)	Difference* Estimate (95% CI)
Global Z	No diabetes	**-0.72 (-0.84, -0.61)**	(reference)	**-0.73 (-0.85, -0.61)**	(reference)
	< 3	**-0.72 (-0.93, -0.50)**	0.01 (-0.19, 0.20)	**-0.85 (-1.16, -0.54)**	-0.12 (-0.43, 0.20)
	3 - 6	**-0.58 (-0.77, -0.39)**	0.14 (-0.01, 0.30)	**-0.57 (-0.76, -0.37)**	**0.17 (0.01, 0.33)**
	6 - 9	**-0.88 (-1.09, -0.67)**	-0.16 (-0.34, 0.02)	**-0.90 (-1.12, -0.69)**	-0.17 (-0.36, 0.01)
	> 9	**-1.06 (-1.40, -0.71)**	**-0.33 (-0.66, -0.00)**	**-1.08 (-1.43, -0.73)**	-0.35 (-0.68, -0.01)
	p-value-for-trend	0.100	-	0.076	-
DWRT	No diabetes	**-0.88 (-1.10, -0.66)**	(reference)	**-0.87 (-1.09, -0.65)**	(reference)
	< 3	**-0.77 (-1.12, -0.42)**	0.11 (-0.18, 0.41)	**-0.86 (-1.29, -0.43)**	0.01 (-0.39, 0.41)
	3 - 6	**-0.74 (-1.06, -0.43)**	0.14 (-0.10, 0.38)	**-0.66 (-0.99, -0.34)**	0.21 (-0.05, 0.46)
	6 - 9	**-0.92 (-1.27, -0.57)**	-0.04 (-0.32, 0.24)	**-0.86 (-1.23, -0.49)**	0.01 (-0.29 0.31)
	> 9	**-1.16 (-1.63, -0.68)**	-0.27 (-0.71, 0.16)	**-1.12 (-1.64, -0.60)**	-0.25 (-0.73, 0.23)
	p-value-for-trend	**0.004**	-	0.987	-
DSST	No diabetes	**-0.59 (-0.67, -0.51)**	(reference)	**-0.60 (-0.68, -0.52)**	(reference)
	< 3	**-0.70 (-0.85, -0.55)**	-0.11 (-0.25, 0.04)	**-0.77 (-0.97, -0.57)**	-0.17 (-0.37, 0.03)
	3 - 6	**-0.63 (-0.77, -0.50)**	-0.04 (-0.16, 0.07)	**-0.63 (-0.76, -0.49)**	-0.03 (-0.14, 0.08)
	6 - 9	**-0.76 (-0.91, -0.61)**	**-0.17 (-0.30, -0.04)**	**-0.79 (-0.95, -0.63)**	**-0.19 (-0.33, -0.05)**
	> 9	**-0.77 (-0.99, -0.56)**	-0.18 (-0.39, 0.02)	**-0.75 (-0.97, -0.52)**	-0.15 (-0.37, 0.07)
	p-value-for-trend	**0.004**	-	**0.007**	-
WFT	No diabetes	**-0.19 (-0.28, -0.10)**	(reference)	**-0.21 (-0.31, -0.11)**	(reference)
	< 3	-0.15 (-0.34, 0.04)	0.04 (-0.14, 0.23)	**-0.27 (-0.51, -0.02)**	**-0.06 (-0.31, 0.20)**
	3 - 6	-0.05 (-0.21, 0.11)	0.14 (-0.00, 0.28)	-0.08 (-0.25, 0.09)	0.13 (-0.02, 0.28)
	6 - 9	**-0.37 (-0.55, -0.19)**	**-0.18 (-0.34, -0.01)**	**-0.43 (-0.62, -0.24)**	**-0.22 (-0.39, -0.06)**
	> 9	**-0.45 (-0.67, -0.23)**	**-0.26 (-0.46, -0.05)**	**-0.46 (-0.68, -0.24)**	**-0.25 (-0.45, -0.05)**
	p-value-for-trend	**0.043**	-	**0.016**	-

* Calculated as the difference in 14-year decline between persons with no diabetes at either visit and persons who have prevalent diabetes at visit 2 or develop diabetes between visits 2 and 4 (negative values indicate greater decline in those with prevalent or incident diabetes)
Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=3,609 total records, with N=2,289 at visit 4(N=498 with diabetes) and N=1,320 at visit 5(N=206 with diabetes).

Supplemental Table 5: ARIC population visit 2 baseline characteristics by diabetes status, propensity score matched cohort

	Total (**N=3,648**)	Diabetes (**N=1,824**)	No Diabetes (**N=1,824**)
Age	58.3 (5.7)	58.2 (5.7)	58.4 (5.7)
Female, %	56.6	57.1	56.1
Visit 5 Attendance, %			
Died before visit 5	40.3	46.7	33.3
Alive, but did not attend	30.5	28.3	32.9
Attended	29.2	25.0	33.8
Race-Center, %			
Minneapolis - White	14.9	14.3	15.6
Washington County - White	16.1	16.4	15.0
Forsyth - White	39.8	40.2	40.7
Forsyth - Black	4.8	4.8	4.7
Jackson - Black	24.3	24.2	24.1
Cognitive scores			
Global cognitive Z score	-0.45 (1.0)	-0.52 (1.0)	-0.38 (1.0)
Delayed word recall test, number of words Recalled	6.2 (1.6)	6.1 (1.6)	6.4 (1.6)
Digit symbol substitution test, number of symbols translated	37.5 (14.6)	36.9 (14.5)	38.5 (14.8)
Word fluency test, number of words generated	29.3 (12.5)	29.3 (12.4)	29.6 (12.5)
Hemoglobin A1c	6.8 (1.9)	8.0 (2.1)	5.6 (0.4)
Prevalent coronary heart disease, %	11.2	11.0	11.3
Prevalent stroke, %	3.9	4.3	3.8
Apolipoprotein E ε4 alleles, %			
0	66.0	67.6	63.4
1	28.2	27.0	30.3
2	3.1	2.8	3.3
Not reported	2.7	2.6	3.0
Hypertension, %	59.0	58.9	59.8
Body mass index, kg/m^2	31.2 (6.3)	31.4 (6.1)	30.9 (6.5)
Total cholesterol level, mg/dL	214 (43.1)	216 (45.4)	211 (40.4)
HDL cholesterol level, mg/dL	45.7 (15.2)	43.1 (14.2)	48.4 (15.8)
Triglyceride level, mg/dL	156 (114.7)	179 (136.0)	132 (79.2)
Education, %			
Less than high school	36.4	35.0	36.5
High school, graduate equivalence degree, or vocational school	37.2	37.8	37.0
College, graduate, or professional school	26.5	27.2	26.5
Cigarette smoking status, %			
Current	22.2	20.8	22.0
Former	36.8	37.4	37.0
Never	41.0	41.8	41.0
Alcohol consumption, %			
Current	36.3	36.2	35.9
Former	33.1	33.3	33.2
Never	30.6	30.4	30.9

Notes: shaded lines represent variables on which matching was performed. There was no significant difference between persons with and without diabetes on the matched variables (p-

values>0.4, and means/proportions were very similar between groups). Propensity scores were developed using logistic regression and included sex, age, race-center, education, cigarette smoking, drinking status, hypertension status, prevalent CHD, prevalent stroke, and body mass index, starting with 13,766 participants at baseline, including those with "not reported" APOE status. All variables were significant. We used psmatch2 in Stata to select matches based on propensity score, with nearest neighbor selected without replacement, using a caliper set to .05, which was 0.5 times the propensity score standard deviation (on the probability scale). All but 3 persons with diabetes had a match.

Supplemental Table 6: Average difference in 20-year decline in global cognitive Z score, delayed word recall, digit symbol substitution, and word fluency among persons with a history of diagnosed diabetes compared to persons without diabetes, for participants of the matched cohort

Test	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference* Estimate (95% CI)
Global Z	**-0.82 (-0.89, -0.75)**	**-0.96 (-1.04, -0.87)**	**-0.14 (-0.23, -0.06)**
Delayed Word Recall Test	**-1.11 (-1.22, -0.99)**	**-1.10 (-1.23, -0.97)**	0.00 (-0.13, 0.14)
Digit Symbol Substitution Test	**-0.70 (-0.75, -0.65)**	**-0.83 (-0.89, -0.78)**	**-0.13 (-0.19, -0.07)**
Word Fluency Test	**-0.17 (-0.23, -0.10)**	**-0.28 (-0.35, -0.21)**	**-0.12 (-0.19, -0.04)**

* Calculated as the difference in 20-year decline between persons without and with diabetes (negative values indicate greater decline in persons with diabetes)
Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype (including those not reporting genotype), and interactions between all of these covariates and time. N=7,472 total records, with N=3,648 participants at visit 2(N=1,824 with diabetes), N=2,670 at visit 4(N=1,244 with diabetes), and N=1,154 at visit 5(N=456 with diabetes)

Supplemental Table 7: Average difference in 20-year decline in global cognitive Z score, delayed word recall, digit symbol substitution, and word fluency among persons with a history of diagnosed diabetes compared to persons without diabetes, censoring cognitive values of participants after they experience a stroke

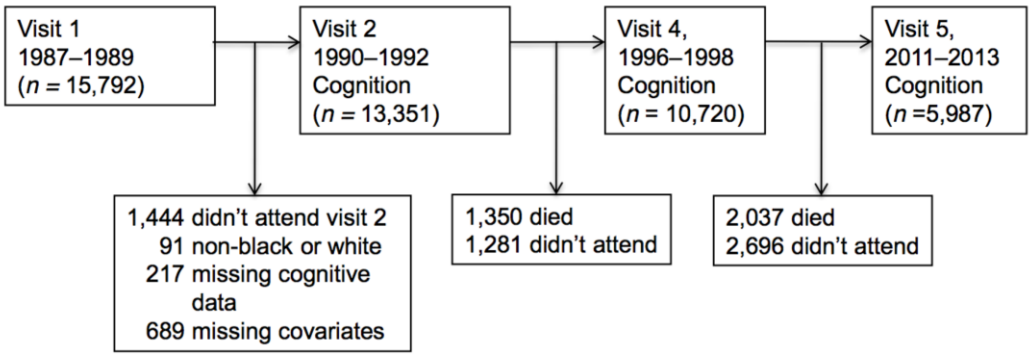
Test	20 year decline – No diabetes Estimate (95% CI)	20 year decline – Diabetes Estimate (95% CI)	Difference Estimate (95% CI)
Global Z	**-0.77 (-0.79, -0.74)**	**-0.91 (-0.98, -0.84)**	**-0.13 (-0.20, -0.06)**
Delayed Word Recall Test	**-0.99 (-1.03, -0.95)**	**-1.03 (-1.15, -0.92)**	-0.04 (-0.16, 0.07)
Digit Symbol Substitution Test	**-0.69 (-0.71, -0.67)**	**-0.82 (-0.87, -0.77)**	**-0.13 (-0.17, -0.08)**
Word Fluency Test	**-0.16 (-0.18, -0.14)**	**-0.26 (-0.32, -0.20)**	**-0.10 (-0.16, -0.04)**

* Calculated as the difference in 20-year decline between persons without and with diabetes (negative values indicate greater decline in persons with diabetes)

† Calculated as the difference expressed as a percentage of the decline in those without diabetes. That is, (decline in participants without diabetes – decline in participants with diabetes)/(decline in participants without diabetes); thus a value of 19% indicates a 19% greater decline in those with diagnosed diabetes compared to those without.

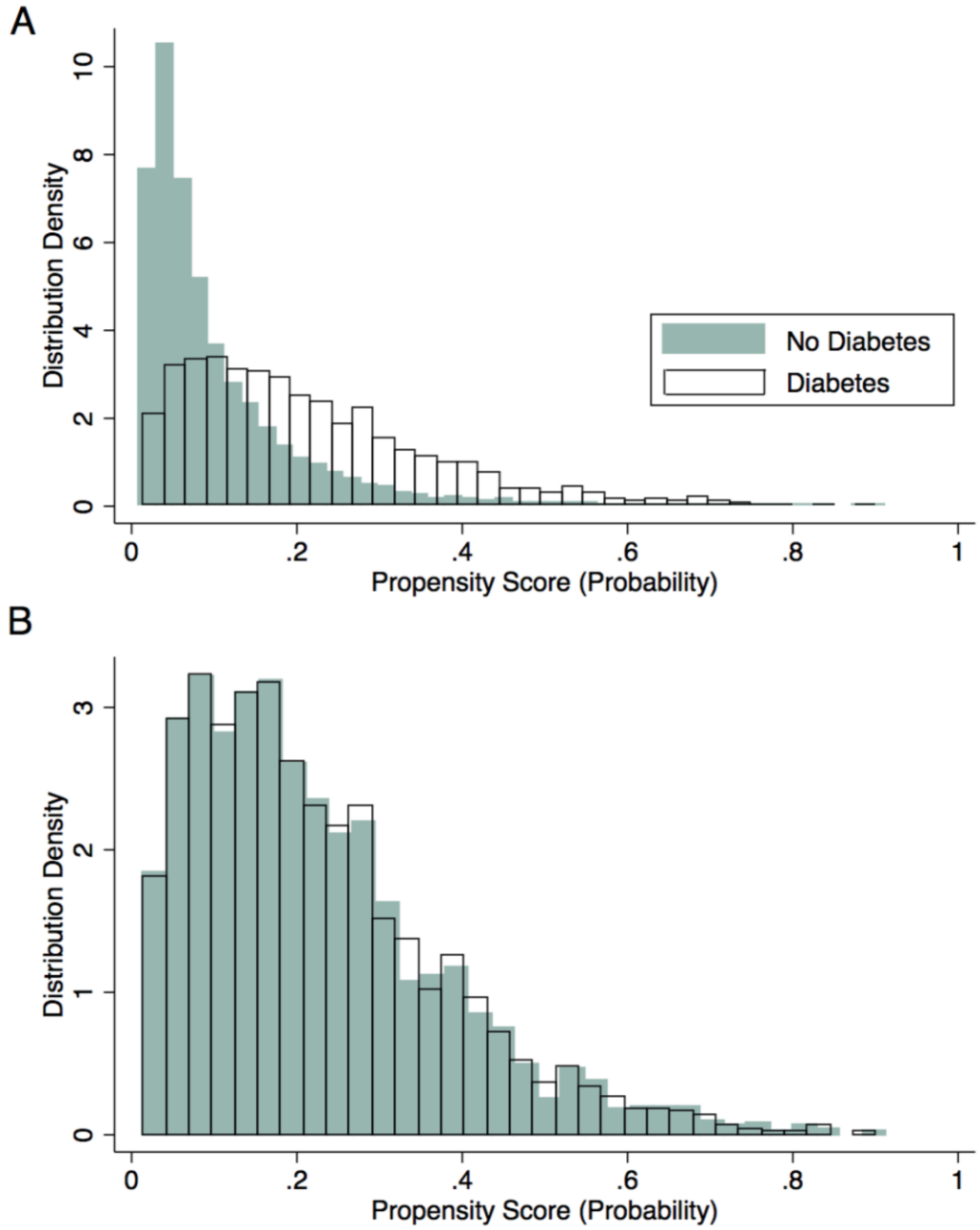
Note: bold values indicate p-value < 0.05. Z scores can be interpreted as standard deviations above or below the mean. For example, a Z score difference of -0.15 means that, on average, persons with diabetes declined an additional 0.15 standard deviations compared to persons without diabetes. Time since baseline was the time metric, and cognitive function was modeled using generalized linear models fit using generalized estimating equations, with adjustment for age, age squared, race-center, sex, education, cigarette smoking, alcohol consumption, body mass index, hypertension, history of coronary heart disease, history of stroke, APOE ε4 genotype, and interactions between all of these covariates and time. N=29,713 total records, with N=13,314 participants at visit 2 (N=1,762 with diabetes), N=10,596 at visit 4(N=1,174 with diabetes), and N=5,803 at visit 5(N=412 with diabetes).

Supplemental Figure 1: Flowchart of study visits and exclusions and pattern of attendance



	Visit 2	Visit 4	Visit 5	Total count (for pattern)
Pattern of visit attendance (X=attended)	X	X	X	5,659
	X	X		5,061
	X			2,303
	X		X	328
Total counts (for visit)	13,351	10,720	5,987	

Supplemental Figure 2: Propensity score distribution for persons with and without diabetes



Legend: Panel A: propensity score distribution for all cohort participants (N=13,351). Panel B: propensity score distribution for matched participants(N=1,824 in each group). Propensity scores are calculated from logistic models that included sex, age, race-center, education, cigarette smoking, drinking status, hypertension status, prevalent CHD, prevalent stroke, and body mass index, starting with 13,766 participants at baseline, including those with "not reported" APOE status. All variables were significant. We used psmatch2 in Stata to select matches based on propensity score, with nearest neighbor selected without replacement, using a caliper set to .05. All but 3 persons with diabetes from the full cohort had a match.

Supplemental Text 1: Summary of Propensity Score Methods

Persons with diabetes differ from those without diabetes on a number of demographic, behavioral, and clinical characteristics. In studying diabetes as a risk factor, a lack of comparability in participant characteristics between the two groups may reduce the effectiveness of controlling for confounding using conventional statistical methods, such as regression, potentially leading to bias. An alternative to the conventional methods to control for cofounding is propensity score matching, a method of treating observational data in an attempt to mimic characteristics of a randomized trial. That is, conditional on the propensity score, baseline characteristics will be similar among the two groups. We used propensity score matching to test the robustness of our findings.

In this propensity score analysis, we modeled diabetes as an outcome using logistic regression and included sex, age, race-center, education, cigarette smoking, drinking status, hypertension status, prevalent coronary heart disease, prevalent stroke, and body mass index. These variables are strongly associated with diabetes and were different between persons with and without diabetes in our study population (Table 1). For this analysis we included an additional 415 participants with "not reported" apolipoprotein E ε4 at baseline, giving 13,766 available participants (N=1,827 with diabetes). Using this model, we predicted the probability of diabetes (propensity score).

For the propensity score, we used nearest neighbor matching without replacement with a caliper of 0.05 (on the probability scale) to select matches among persons without diabetes. A caliper of 0.05 was chosen because it is half of the standard deviation of our propensity score, which is indicated by prior research to remove a substantial portion of the initial bias (Rubin and Thomas, 1996). All but 3 participants with diabetes had a match, giving N=1,824 participants with diabetes, compared to N=1,779 in our primary regression analysis.

The propensity score distributions for persons with and without diabetes in the full cohort of 13,766 participants are shown in eFigure 2, Panel A, along with the propensity score distribution among matched participants (eFigure 2, Panel B). In the full cohort (eFigure 2, Panel A) the propensity scores for persons with and without diabetes overlapped across the full range of probabilities, suggesting that the conventional regression approach was sufficient in this case.

After matching, the propensity scores overlap fully (eFigure 2, Panel B), suggesting that the propensity score matching performed well. In addition, Supplemental Table 5 shows baseline characteristics among matched participants. Visual inspection of the means and percentages showed the matched factors (the gray-shaded lines) were well balanced; we found no significant differences between persons with and without diabetes on matched characteristics (p-values>0.4).

When we used the matched sample to examine the relationship between diabetes and cognitive decline (Supplemental Table 6), our results were not appreciably different and our conclusions were unchanged from the primary regression analysis (Table 2).

Reference
Rubin, D. B., & Thomas, N. (1996). Matching using estimated propensity scores: relating theory to practice. *Biometrics, 52*(1), 249-264.

Supplemental Text 2: Inverse probability of attrition weighting (IPAW) details

Persons with diabetes and those with substantial cognitive impairment are more likely to drop out of the study or die before the next study visit, potentially biasing the estimated relationship between diabetes and cognitive decline. Inverse probability of attrition weighting (IPAW) is a method to account for this differential dropout.

We developed stabilized inverse probability of attrition weights for each individual at each time point of participation and used weighted analyses to obtain estimates "adjusted" for attrition. These weights are calculated from predicted probabilities of attrition estimated from two sets of logistic models, one set for dropout due to attrition, and one for dropout due to death.

For death, we modeled the probability of death between visits 2 and 4, between visits 4 and a pseudo visit (based on annual phone call data between visits 4 and 5), and between the pseudo visit and visit 5. For non-death drop-out, we modeled the probability of drop out between visits 2 and 4 and between visits 4 and 5. All models used the same covariates, updated to reflect current status or total history, which were selected for inclusion into prediction models using a stepwise selection criterion. Models were run separately for black and white participants.

Covariates included: age, sex, center, education, diabetes, APOE ε4 alleles (0,1,2), history of stroke, history of coronary heart disease, cigarette smoking, body mass index, height, hypertension medication use, global z score (categorized into quintiles), self-reported poor health (measured at visit 1), number of prior hospitalizations, retirement status, chronic lung disease, lung capacity, insurance status, white blood cell count, anemia, and interactions between age and global z score, anemia, and lung volume.

To calculate the stabilized weights, we ran additional models predicting death and dropout using a subset of covariates, namely age, sex, center, education, and diabetes. The probabilities from these models were multiplied by the weights calculated above to create stabilized weights. Ideally these weights have a mean of 1 and represent the distribution of the original population without inflating the sample size. Additional information regarding probability weighting can be found in (Hernan, 2000).

The table below shows the distribution of the stabilized weights. For completeness, we show the unstabilized weights though they were not used in our analyses.

Distribution of stabilized and unstabilized weights, by race:

	Mean	Standard deviation	Minimum	5^{th} percentile	95^{th} percentile	Maximum
Black						
Unstabilized	1.504	1.652	1.000	1.000	2.790	82.18
Stabilized	1.010	0.273	0.125	0.770	1.301	9.123
White						
Unstabilized	1.320	1.999	1.000	1.000	2.200	243.0
Stabilized	1.002	0.296	0.282	0.830	1.159	19.24

Reference
Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology. 2000 Sep;11(5):561-70.

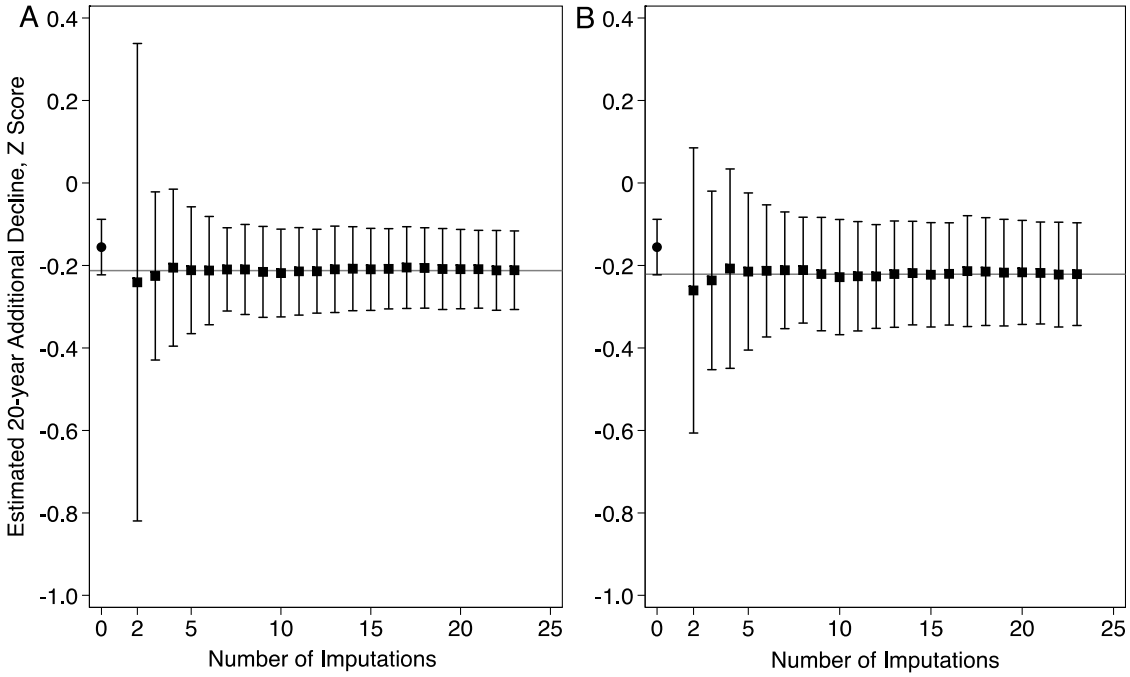
Supplemental Text 3: Transformation of Global Z-score into an "age equivalent"

To put our main results for the Global Z-score difference of -0.15 into context, we calculated the age-related equivalent for this degree of decline. To do this, we used our final model to estimate how much older someone without diabetes would need to be, at baseline, to perform 0.15 Z scores lower, and we estimated that to be 4.9 years. That is, our model of Z scores included age, and at baseline older participants performed worse than younger participants (ie negative coefficient for age). The coefficient for age was -0.02998, so each additional year of being older at baseline reduced Z scores by ~0.03. Thus being about 5 years older at baseline (without diabetes) was "equivalent" to the amount of additional decline over 20 years among persons with diabetes.

Also because 0.15 may not be intuitive, we categorized the decline as percent additional decline among persons with diabetes. That is, persons without diabetes had -0.78 z-score decline over 20 years, and persons with diabetes -0.93 (table 2). Therefore persons with diabetes had (0.15)/0.78 = 19% faster decline than persons without diabetes.

APPENDIX B: Supplemental material for Chapter 2

Supplemental Figure 1. Estimated 20-year additional decline in persons with diabetes compared to those without, by number of imputations



Legend:
Estimates and 95% CIs are for mixed-effects models using time since baseline as the time axis, modeled using a spline term with a knot at 6 years, the median time between visits 2 and 4. Random effects were random intercept and two random slopes, one for each time spline term. All models were adjusted for age, age squared, race-field center (Maryland (white race); Minnesota (white race); North Carolina (white race); North Carolina (black race); Mississippi (black race)), sex, education (less than high school; high school, high school equivalent, or vocational school; or college, graduate, or professional school), cigarette smoking status (current; former; never), alcohol consumption status (current; former; never), body mass index (kg/m^2), hypertension (yes or no), history of stroke (yes or no), apolipoprotein E ε4 genotype (0, 1, or 2 alleles). Interaction terms between the time spline terms and age, sex, race-field center, education, history of stroke, and apoliprotein E ε4 genotype were also included in the model. Imputations were generated by chained equations. **Panel A:** Imputing values for participants alive at visit 5. **Panel B:** Imputing values for participants alive and deceased by visit 5.

Supplemental Table 1: Characteristics of study participants with suspected dementia, by clinical dementia rating (CDR) status

	Has CDR	No CDR obtained	p-value for difference
N (%)	751	711	-
Age, years	60.7 (5.1)	60.5 (5.2)	0.554
Female, %	57.0	59.5	0.334
Black, %	24.8	28.0	0.162
HbA1c, %	5.9 (1.3)	6.1 (1.5)	0.100
Diabetes, %	18.8	21.1	0.271
Body mass index, kg/m^2	28.0 (5.0)	28.1 (5.3)	0.552
History of CHD, %	6.0	5.5	0.678
History of stroke, %	2.3	3.4	0.198
Hypertension, %	41.0	47.0	0.022
APOE e4 alleles, %			
0	54.4	54.6	0.947
1	38.3	38.2	0.953
2	7.2	7.2	0.985
Education, %			
Less than high school	30.1	31.2	0.640
High school	38.1	38.8	0.773
College/vocational	31.8	30.0	0.441
Smoking, %			
Current	19.5	20.8	0.512
Former	37.6	36.3	0.618
Never	42.9	42.8	0.964
Drinking, %			
Current	46.9	48.6	0.526
Former	25.2	24.2	0.666
Never	27.9	27.2	0.770
Measures of Cognitive Function			
Global Z	-0.26 (0.97)	-0.35 (1.04)	0.067
DWRT, words recalled	6.2 (1.5)	6.1 (1.7)	0.417
DSST, number completed	40.8 (14.1)	39.8 (13.8)	0.177
WFT, words generated	32.3 (12.2)	30.8 (12.6)	0.022

All characteristics shown were measured at baseline (visit 2), except education, which was collected at visit 1. Values shown as %, or mean (SD)

Abbreviations: CHD, coronary heart disease; DWRT, delayed word recall test; DSST, digit symbol substitution test; WFT, word fluency test; CDR, clinical dementia rating.

Supplemental Text 1: Model specifications for simulations

The model used to generate Z scores is shown below, and was used for all scenarios. It is worth noting that suspect dementia was built into our data generating model in our simulations, but was not included in our mixed model. This was necessary because CDR data were specifically sought for persons with suspect dementia, because of the distinct characteristics of these participants, and because including it allowed us to retain the correlations between risk factors and cognitive decline. That is, because we retained all covariates from ARIC, in generating "believable" Z scores, we needed a way to identify participants who would ultimately experience cognitive decline, such that their risk factors, CDR values, TICS, etc would correspond with observed covariates (diabetes, hypertension, etc).

```
global Z = -0.1*timesp1 - 0.3*timesp2 - 1*educ1 - 0.43*educ2 - 0.005*bmi21c
       + 0.12*rc_0 - 0.74*rc_1 + 0.07*rc_2 - 0.39*rc_3 + 0.004*female - 0.03*agev2c
       - 0.5*suspect_dem - 0.01*timesp1*suspect_dem - 0.4*timesp2*suspect_dem
       - 0.024*htn - 0.025*timesp1*htn - 0.05*timesp2*htn
       - 0.15*diabstrat - 0.05*timesp1*diabstrat - 0.05*timesp2*diabstrat
       - 0.15*smkv2 - 0.01*timesp1*smkv2 - 0.01*timesp2*smkv2
       + u0i + u1i*timesp1 + u2i*timesp2 + rhi

       u0i ~ N(0, 0.6)
       u1i ~ N(0, 0.2)
       u2i ~ N(0, 0.2)
       rhi ~ N(0, 0.4)
```

We fit the above model using observed ARIC cohort data, and the resulting coefficients (with rounding) in the above simulation model.

Description of variables:
timesp1, timesp2: spline terms for time (years since visit 2, the baseline visit), with the knot at 6 years. The spline terms are modeled per 6 years, such that the coefficient of timesp1 represents average decline between visits 2 and 4 (6 years is the average time between the two visits)
educ1: less than high school education
educ2: high school, high school equivalent, or vocational school
educ3: college, graduate, or professional school (reference)
bmi21c: body mass index, centered at 28 kg/m^2
rc_*: race-field center (rc_0, Minnesota whites; rc_1, Mississippi blacks; rc_2, Maryland whites; rc_3, North Carolina blacks; rc_4, North Carolina whites (reference))
female: female sex (yes/no)
agev2c: age at visit 2, centered at 57 years
suspect_dem: suspected dementia (yes/no)
htn: hypertension (yes/no)
diabstrat: diabetes (yes/no)
smkv2: current smoker (yes/no)
u0i: random intercept for participant *i*
u1i, u2i: random slopes for each time spline for participant *i*
rhi: residual error for participant *i* at time *h* (visits 2, 4, and 5)

The probabilities of death and dropout were modeled using multinomial logistic regression. The outcomes are 1) attended visit 5 (reference category), 2) alive but did not attend, and 3) deceased. Intercepts for the models were chosen such that the average proportions of death and dropout were similar to those observed in ARIC. That is, 29.08% of baseline participants were deceased by visit 5, and of the remaining living participants, 37.36% did not attend visit 5.

Models used to simulate death and dropout:

Scenario	Death	Dropout out
1 MCAR	Probability fixed: 0.2908	Probability fixed: 0.3736
2 MAR	Probability using a multinomial logistic model: -1.61 - .536*globalz_v4 + 0.711*diabstrat + 0.529*htn + 0.796*smkv2	Probability using a multinomial logistic model: -0.7 - 0.224*globalz_v4 - 0.054*globalz_v2 + 0.333*diabstrat + 0.316*htn + 0.298*smkv2
3 MAR for MICE	Probability using a multinomial logistic model: -1.635 - 0.536*globv4 + 0.711*diabstrat + 0.529*htn + 0.796*smkv2 + 0.25*suspect_dem	Probability using a multinomial logistic model: -0.75 - 0.224*globv4 - 0.054*globv2 + 0.333*diabstrat + 0.316*htn + 0.5*suspect_dem
4 MNAR	Probability fixed: 0.4	Probability = 0.8 if simulated global Z at visit 5 is < 25th percentile. Probability = 0.5 for everyone else

globalz_v2: simulated global z at visit 2
globalz_v4: simulated global z at visit 4

The primary Stata commands used were “mi impute chained” to perform the imputations and “mi estimate:” to run longitudinal models using the imputed values.

Supplemental Table 2: Simulation results of estimated 20-year additional decline for persons with diabetes compared to those without, considering only participants alive at visit 5

		Truth		Imputation
Scenario		Living Participants	Available case	Living Participants
1 MCAR	Mean effect (SE)	-0.236 (0.028)	-0.235 (0.035)	-0.231 (0.034)
	Bias (%)	-	-0.001 (0%)	-0.005 (2%)
	Empirical SE	0.0261	0.0341	0.0322
	CI coverage	-	100%	100%
2 MAR	Mean effect (SE)	-0.229 (0.031)	-0.225 (0.042)	-0.221 (0.043)
	Bias (%)	-	-0.004 (2%)	-0.008 (4%)
	Empirical SE	0.0309	0.0402	0.0389
	CI coverage	-	95%	95%
3 MAR for MICE, MNAR for available case	Mean effect (SE)	-0.215 (0.031)	-0.182 (0.042)	-0.208 (0.044)
	Bias (%)	-	-0.033 (15%)	-0.007 (3%)
	Empirical SE	0.0298	0.0436	0.0448
	CI coverage	-	94%	98%
4 MNAR	Mean effect (SE)	-0.222 (0.028)	-0.168 (0.035)	-0.174 (0.037)
	Bias (%)	-	-0.053 (24%)	-0.047 (21%)
	Empirical SE	0.0249	0.0341	0.0308
	CI coverage	-	72%	85%

Mean effect is an average of 100 simulations. The standard error (SE) of the mean effect is the square root of mean variances across 100 simulations. Bias is calculated as the mean effect estimate from each method (available case, imputation in living participants) minus the mean effect estimate from the truth. Negative values indicate underestimation of the true effect and positive values represent overestimation. Bias % is calculated as the estimated bias divided by the true effect (ie 0.005/0.236 = 2%). The empirical SE is the standard deviation of the mean effect across 100 simulations. CI coverage is the percentage of the simulations where the confidence interval for the estimated effect includes the true effect.

Scenario 1: Death and dropout simulated to be missing completely at random, with probabilities of 0.29 and 0.37, respectively, chosen to match proportions observed in ARIC

Scenario 2: Death and dropout simulated to depend on prior visit global Z score, diabetes, hypertension, and current smoking status

Scenario 3: Death and dropout simulated to depend on prior visit global Z score, diabetes, hypertension, current smoking status, and suspected dementia. As a result, the "complete case", which uses a mixed model, is MNAR (suspect dementia not included in the mixed model), but MICE is MAR (suspect dementia is included for imputation). This scenario is consistent with what we believe the true missingness pattern in ARIC to be

Scenario 4: Dropout simulated to depend on visit 5 global Z scores (i.e. unobserved scores), and death simulated to be missing completely at random

APPENDIX C: Supplemental material for Chapter 3

Supplemental Table 1. Adjusted HRs (95% CI) for the association of 1,5-anhydroglucitol categories with incident dementia – stratified analyses by diabetes and HbA1c category

		Events/N	Model 1 HR (95% CI)	p-value†	Model 2 HR (95% CI)	p-value†
No Diabetes						
	1,5-AG ≥10	829/10708	1 (reference)	0.959	1 (reference)	0.717
	1,5-AG <10	48/576	1.01 (0.75, 1.35)		1.06 (0.79, 1.42)	
Diabetes						
HbA1c < 7%	1,5-AG ≥10	60/535	1 (reference)	0.400	1 (reference)	0.202
	1,5-AG <10	19/125	1.26 (0.74, 2.15)		1.45 (0.82, 2.56)	
Diabetes						
HbA1c ≥ 7%	1,5-AG ≥10	19/176	1 (reference)	0.035	1 (reference)	0.110
	1,5-AG <10	130/876	1.68 (1.04, 2.73)		1.53 (0.91, 2.58)	

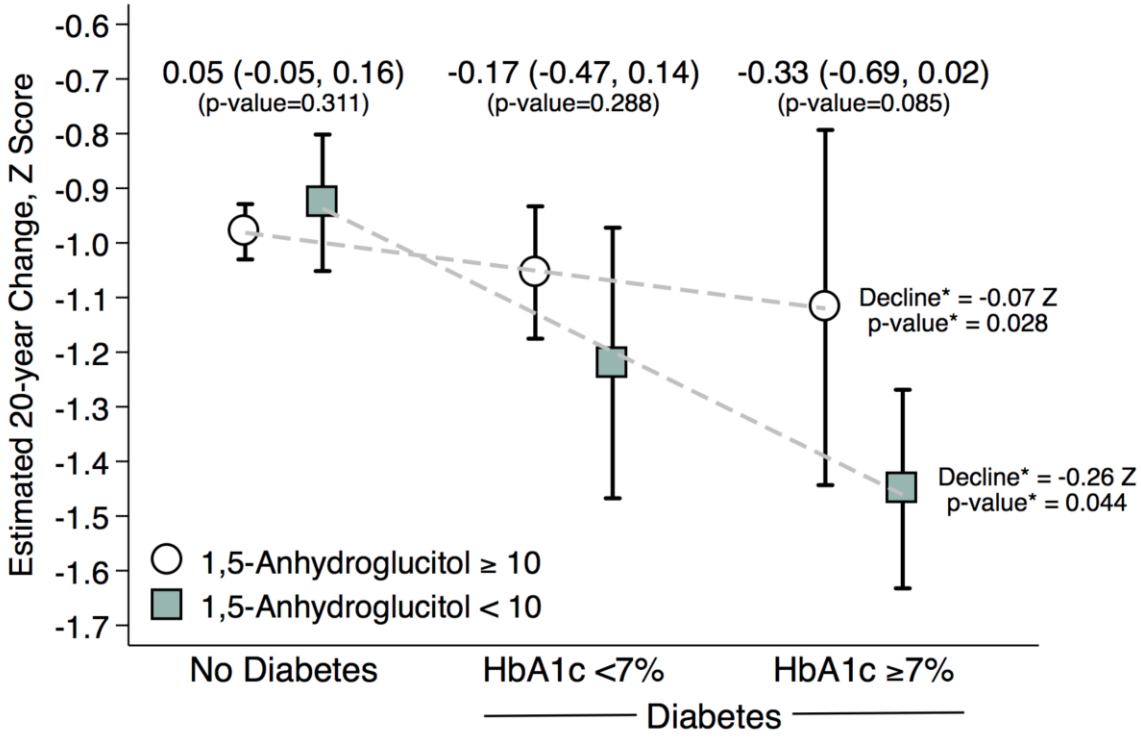
Hazard ratios (HRs) and 95% confidence intervals (CI) are from Cox proportional hazards regression
Model 1: Adjusted for age, sex, education, and race-center
Model 2: Adjusted for the variables in model 1 plus hypertension, history of stroke, history of coronary heart disease, cigarette smoking status, drinking status, APOE4, and HbA1c
Diabetes was defined as a self-reported physician diagnosis of diabetes, use of glucose lowering medication, or an HbA1c ≥ 6.5%
† p-values compare 1,5-AG ≥10 μg/mL to 1,5-AG <10 μg/mL within diabetes status and HbA1c category

Supplemental Table 2. Adjusted HRs (95% CI) for the association of 1,5-anhydroglucitol categories with incident dementia by diabetes status among ARIC participants with at least one hospitalization, N=10,646

		Events/N	Model 1 HR (95% CI)	p-value†	Model 2 HR (95% CI)	p-value†
No Diabetes						
	1,5-AG ≥10	792/8589	1 (reference)	0.793	1 (reference)	0.567
	1,5-AG <10	44/473	1.05 (0.73, 1.51)		1.11 (0.77, 1.60)	
Diabetes						
HbA1c < 7%	1,5-AG ≥10	57/483	1.33 (0.96, 1.83)	0.881	1.28 (0.92, 1.78)	0.730
	1,5-AG <10	19/119	1.39 (0.80, 2.43)		1.43 (0.82, 2.51)	
HbA1c ≥ 7%	1,5-AG ≥10	19/159	1.48 (0.85, 2.57)	0.227	1.29 (0.72, 2.32)	0.122
	1,5-AG <10	125/823	2.11 (1.69, 2.63)		2.08 (1.36, 3.19)	

Model 1: Adjusted for age, sex, education, and race-center
Model 2: Adjusted for the variables in model 1 plus hypertension, history of stroke, history of coronary heart disease, cigarette smoking status, drinking status, and APOE4
***** Diabetes was defined as a self-reported physician diagnosis of diabetes, use of glucose lowering medication, or an HbA1c ≥ 6.5%
† p-values compare 1,5-AG ≥10 μg/mL to 1,5-AG <10 μg/mL within diabetes status and HbA1c category

Supplemental Figure 1: Estimated association between baseline categories of diabetes and 20-year cognitive decline, by diabetes, HbA1c, and 1,5-Anhydroglucitol group, excluding participants with baseline scores below the 5th percentile



Legend: Estimates and 95% confidence intervals are from mixed-effects models with adjustment for age, age^2, race-field center, sex, education, cigarette smoking status, drinking status, hypertension, history of stroke, history of coronary heart disease, apolipoprotein E ε4 genotype, body mass index, and interactions between these variables and time. Time since baseline was the time axis, and was modeled with a linear spline with a knot at 6 years. A random intercept and two random slopes for time (one for each spline term) were included, and the three random effects were assumed to be independent. *Dashed lines indicate linear regression fit across the three diabetes groupings (no diabetes, diabetes HbA1c<7%, diabetes HbA1c ≥7%) and 1,5-AG category. Decline indicates the estimated decline per category and the p-value is for the estimated decline across categories.

APPENDIX D: Supplemental material for Chapter 4

Supplemental Table 1. Standardized factor loadings and fit statistics for invariance models by age

	Configural Invariance Variances constrained to 1, means to 0; intercepts, residuals, and factor loadings unconstrained		**Metric Invariance** Variances constrained to 1, means to 0, factor loadings invariant across groups; intercepts and residuals unconstrained		**Strong Invariance** Variances constrained to 1, means to 0, factor loadings and intercepts invariant across groups; residuals unconstrained		**Strict Invariance** Variances constrained to 1, means to 0, factor loadings, intercepts, and residuals invariant across groups	
Memory	<75	≥75	<75	≥75	<75	≥75	<75	≥75
DWR	0.57	0.65	0.60	0.62	0.61	0.63	0.59	0.66
LM 1	0.64	0.71	0.65	0.70	0.65	0.70	0.65	0.71
LM 2	0.67	0.73	0.67	0.73	0.67	0.74	0.67	0.73
Incidental Learning	0.60	0.65	0.56	0.68	0.55	0.67	0.57	0.64
Language								
Animal Naming	0.67	0.73	0.66	0.74	0.67	0.75	0.68	0.73
Word Fluency	0.70	0.67	0.66	0.70	0.63	0.67	0.62	0.67
Boston Naming	0.62	0.68	0.66	0.60	0.67	0.61	0.62	0.68
SAPS								
Trails A	0.62	0.68	0.65	0.65	0.67	0.67	0.66	0.69
Trails B	0.81	0.82	0.81	0.82	0.80	0.83	0.80	0.83
DSS	0.75	0.80	0.75	0.80	0.75	0.81	0.77	0.79
DSB	0.51	0.50	0.48	0.52	0.46	0.50	0.47	0.49
Fit statistics								
CFI	0.971		0.967		0.961		0.951	
TLI	0.959		0.958		0.955		0.949	
RMSEA*	0.058 (0.055, 0.061)		0.059 (0.056, 0.062)		0.061 (0.058, 0.064)		0.065 (0.062, 0.068)	
SRMR†	0.035		0.040		0.044		0.042	
BIC	158,722		158,776		158,886		159,095	

* RMSEA listed as value (90% confidence interval) † SRMR calculated from models restricted to complete data

Abbreviations: DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC).

Supplemental Table 2. Standardized factor loadings and fit statistics for invariance models by sex

	Configural Invariance Variances constrained to 1, means to 0; intercepts, residuals, and factor loadings unconstrained		**Metric Invariance** Variances constrained to 1, means to 0, factor loadings invariant across groups; intercepts and residuals unconstrained		**Strong Invariance** Variances constrained to 1, means to 0, factor loadings and intercepts invariant across groups; residuals unconstrained		**Strict Invariance** Variances constrained to 1, means to 0, factor loadings, intercepts, and residuals invariant across groups	
Memory	Male	Female	Male	Female	Male	Female	Male	Female
DWR	0.62	0.67	0.63	0.67	0.63	0.67	0.64	0.66
LM 1	0.69	0.72	0.69	0.72	0.68	0.70	0.68	0.70
LM 2	0.72	0.74	0.72	0.74	0.71	0.73	0.71	0.73
Incidental Learning	0.65	0.64	0.64	0.64	0.64	0.64	0.63	0.65
Language								
Animal Naming	0.71	0.74	0.70	0.75	0.70	0.75	0.73	0.73
Word Fluency	0.68	0.66	0.66	0.68	0.65	0.68	0.66	0.67
Boston Naming	0.64	0.70	0.67	0.68	0.67	0.68	0.67	0.67
SAPS								
Trails A	0.68	0.71	0.68	0.70	0.67	0.69	0.68	0.69
Trails B	0.84	0.85	0.83	0.85	0.81	0.83	0.82	0.83
DSS	0.81	0.81	0.82	0.80	0.82	0.80	0.80	0.81
DSB	0.53	0.50	0.50	0.52	0.50	0.52	0.50	0.51
Fit statistics								
CFI	0.975		0.975		0.952		0.950	
TLI	0.966		0.968		0.944		0.948	
RMSEA*	0.056 (0.053, 0.060)		0.055 (0.051, 0.058)		0.072 (0.069, 0.075)		0.069 (0.066, 0.072)	
SRMR†	0.033		0.034		0.047		0.047	
BIC	159,301		159,266		159,955		159,916	

* RMSEA listed as value (90% confidence interval) † SRMR calculated from models restricted to complete data

Abbreviations: DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC).

Supplemental Table 3. Standardized factor loadings and fit statistics for invariance models by race

	Configural Invariance Variances constrained to 1, means to 0; intercepts, residuals, and factor loadings unconstrained		**Metric Invariance** Variances constrained to 1, means to 0, factor loadings invariant across groups; intercepts and residuals unconstrained		**Strong Invariance** Variances constrained to 1, means to 0, factor loadings and intercepts invariant across groups; residuals unconstrained		**Strict Invariance** Variances constrained to 1, means to 0, factor loadings, intercepts, and residuals invariant across groups	
Memory	White	Black	White	Black	White	Black	White	Black
DWR	0.64	0.67	0.64	0.66	0.64	0.66	0.64	0.65
LM 1	0.70	0.71	0.70	0.71	0.70	0.71	0.70	0.71
LM 2	0.73	0.72	0.73	0.73	0.73	0.73	0.73	0.73
Incidental Learning	0.64	0.66	0.64	0.65	0.64	0.65	0.64	0.65
Language								
Animal Naming	0.73	0.74	0.71	0.77	0.71	0.77	0.72	0.75
Word Fluency	0.64	0.78	0.65	0.76	0.65	0.76	0.67	0.70
Boston Naming	0.63	0.77	0.64	0.75	0.64	0.75	0.66	0.69
SAPS								
Trails A	0.68	0.76	0.68	0.75	0.68	0.74	0.69	0.71
Trails B	0.85	0.83	0.84	0.85	0.84	0.84	0.83	0.85
DSS	0.79	0.86	0.79	0.85	0.79	0.85	0.80	0.82
DSB	0.49	0.59	0.50	0.56	0.50	0.56	0.51	0.53
Fit statistics								
CFI	0.971		0.970		0.969		0.964	
TLI	0.960		0.963		0.964		0.963	
RMSEA*	0.061 (0.058, 0.064)		0.059 (0.056, 0.062)		0.058 (0.055, 0.061)		0.059 (0.056, 0.062)	
SRMR†	0.035		0.036		0.040		0.046	
BIC	159,954		159,920		159,909		159,985	

* RMSEA listed as value (90% confidence interval) † SRMR calculated from models restricted to complete data

Abbreviations: DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC).

Supplemental Table 4. Standardized factor loadings and fit statistics for invariance models by education

	Configural Invariance Variances constrained to 1, means to 0; intercepts, residuals, and factor loadings unconstrained			**Metric Invariance** Variances constrained to 1, means to 0, factor loadings invariant across groups; intercepts and residuals unconstrained			**Strong Invariance** Variances constrained to 1, means to 0, factor loadings and intercepts invariant across groups; residuals unconstrained			**Strict Invariance** Variances constrained to 1, means to 0, factor loadings, intercepts, and residuals invariant across groups		
Memory	<HS	HS	>HS	<HS	HS	>HS	<HS	HS	>HS	<HS	HS	>HS
DWR	0.68	0.62	0.66	0.60	0.63	0.68	0.57	0.61	0.65	0.60	0.60	0.64
LM 1	0.63	0.64	0.68	0.61	0.64	0.68	0.63	0.66	0.70	0.66	0.66	0.70
LM 2	0.66	0.67	0.72	0.68	0.68	0.70	0.70	0.69	0.72	0.69	0.69	0.73
Incidental Learning	0.59	0.62	0.64	0.64	0.61	0.63	0.63	0.60	0.63	0.60	0.60	0.64
Language												
Animal Naming	0.70	0.69	0.76	0.76	0.71	0.69	0.70	0.66	0.62	0.67	0.66	0.66
Word Fluency	0.74	0.58	0.59	0.69	0.60	0.59	0.73	0.64	0.61	0.64	0.63	0.63
Boston Naming	0.62	0.61	0.59	0.54	0.55	0.65	0.57	0.58	0.66	0.63	0.62	0.61
SAPS												
Trails A	0.66	0.69	0.63	0.58	0.67	0.66	0.57	0.65	0.65	0.61	0.65	0.64
Trails B	0.76	0.81	0.82	0.80	0.81	0.81	0.80	0.80	0.80	0.77	0.81	0.80
DSS	0.80	0.78	0.75	0.81	0.78	0.75	0.81	0.78	0.75	0.74	0.78	0.77
DSB	0.51	0.44	0.45	0.47	0.47	0.43	0.49	0.49	0.45	0.44	0.48	0.47
Fit statistics												
CFI	0.969			0.963			0.951			0.937		
TLI	0.958			0.955			0.947			0.940		
RMSEA*	0.058 (0.055, 0.061)			0.060 (0.056, 0.063)			0.065 (0.062, 0.068)			0.069 (0.066, 0.072)		
SRMR†	0.038			0.045			0.051			0.050		
BIC	157,780			157,819			158,035			158,256		

* RMSEA listed as value (90% confidence interval) † SRMR calculated from models restricted to complete data

Abbreviations: HS, high school; DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards; CFI, comparative fit index (>0.90 indicates good fit); TLI, Tucker-Lewis index (>0.90 indicates good fit); RMSEA, root mean squared error of approximation (<0.10 indicates good fit, <0.05 indicates very good fit); SRMR, standardized root mean squared residual (<0.08 indicates adequate fit, <0.05 indicates good fit); BIC, Bayesian information criterion (lower numbers are better, and decreases >10 indicate strong evidence to prefer the model with the lower BIC)

Supplemental Table 5: Internal consistency (Cronbach's alpha) of *a priori* hypothesized three-domain structure

	Item-test correlation*	Item-rest correlation†	Alpha‡
Memory			
DWR	0.735	0.508	0.814
LM 1	0.871	0.746	0.696
LM 2	0.889	0.780	0.679
Incidental Learning	0.717	0.491	0.819
Summary alpha			0.807
Language			
Animal Naming	0.827	0.582	0.575
Word Fluency	0.785	0.503	0.681
Boston Naming	0.806	0.544	0.626
Summary alpha			0.718
SAPS			
Trails A	0.817	0.639	0.700
Trails B	0.851	0.702	0.681
DSS	0.844	0.680	0.673
DSB	0.669	0.405	0.815
Summary alpha			0.775

* Item-test correlations show the correlation of individual tests with the domain score.
† Item-rest correlations show the correlation of individual tests with a domain created from the remaining tests.
‡ Values represent summary alphas that result from a domain created after excluding a given test. Summary alpha values are the overall Cronbach's alpha for the domain comprised of the given tests.
Abbreviations: DWR, delayed word recall; LM, logical memory; SAPS, sustained attention and processing speed; DSS, digit symbol substitution; DSB, digit span backwards.

APPENDIX E: Supplemental material for Chapter 5

Supplemental Text 1. Description of neuropsychological tests by cognitive domain

Memory domain

For the DWRT participants were given ten nouns and asked to use each in a sentence. After the administration of the DSST (approximately a five minute delay), the participant was given one minute to recall the ten words. The score on the DWRT was the number of words correctly recalled. The LM tests provide a measure of immediate and delayed verbal recall. For the LM-1, participants were read two short stories, and asked to recall details after being read each story. They were informed they would be asked about the stories again and were asked to remember the details. LM-2 occurred approximately 20 minutes after the completion of LM-1, and participants were asked to again recall the details from the two short stories. The maximum possible score on the LM-1 and LM-2 was 50.

Language domain

During the WFT, participants asked to generate words beginning with F, A, and S, with an allotment of one minute per letter. Proper nouns were not included. The total score was the number of words generated after the three trials. The ANT is a measure of category fluency. Participants were given one minute to name as many animals as possible. Imaginary, magical and extinct animals were allowed, as well as animal breeds and age- or sex-specific animals (eg. buck, doe, fawn). The participant's score was the number of animals named.

Executive function domain

For the DSST, participants were asked to translate digits to symbols using a key within a 90 second time limit. The score was the number of correctly translated pairs, with a maximum possible score of 93. TMT-A consisted of a page with the numbers 1-25 irregularly distributed on a white page. The participants were asked to connect the numbers in sequential order as quickly as possible. TMT-B was similar to TMT-A, however it consisted of both numbers (1-13) and letters (A-L). Participants were asked to connect the numbers and letter in alternating order (e.g. 1-A-2-B-3-C etc). The score for both TMT-A and TMT-B was the number of seconds required to complete the task. If a participant could not complete the task in under 240 seconds, the test was ended and a score of 240 seconds was recorded. Participants who made 5 or more mistakes were also given the maximum score of 240 seconds.

Abbreviations: DWRT, delayed word recall test; DSST, digit symbol substitution test; LM, logical memory; WFT, word fluency test; ANT, animal naming test; TMT, trail making test.

Supplemental Table 1. Additional study population characteristics by diabetes status and HbA1c category, the Atherosclerosis Risk in Communities Study, 2011-2013 (Visit 5)

	No Diagnosed Diabetes				Diagnosed Diabetes	
	Low-Normal HbA1c <5%	Normo-glycemic HbA1c 5-5.6%	Pre-diabetes HbA1c 5.7-6.4%	Un-diagnosed HbA1c ≥6.5%	HbA1c <7%	HbA1c ≥7%
N	106	1,914	1,692	122	1,381	531
Liver Enzymes						
ALT	17.5 (7.2)	18.8 (8.4)	19.4 (9.6)	22.3 (26.1)	20.1 (21.7)	21.8 (13.2)
AST	22.6 (7.0)	23.7 (10.9)	23.5 (8.1)	23.3 (10.6)	23.4 (14.9)	22.3 (10.0)
GGT	26.1 (24.8)	23.4 (19.1)	24.5 (18.9)	30.6 (25.4)	25.6 (20.3)	30.7 (22.6)
C-Reactive Protein, %						
<1 mg/L	34.0	30.1	24.8	12.4	24.4	17.1
1-3 mg/L	39.6	39.3	37.3	38.2	36.0	34.5
≥3 mg/L	26.4	30.6	37.9	49.4	39.6	48.4
Fasting Insulin, µU/mL	10.6 (6.5)	11.0 (7.5)	13.6 (8.7)	17.8 (9.6)	15.4 (11.9)	21.0 (37.6)
Hypolipidemia*, %						
Low LDL-c	10.6	5.4	7.0	7.0	17.4	17.9
Low HDL-c	13.5	5.5	6.0	9.2	12.8	18.2
Low Total cholesterol	11.5	6.2	7.0	5.8	17.0	15.5
Low Triglycerides	18.3	12.2	8.3	6.9	9.3	5.2
HbA1c Visit 2 (1990-1992)†	4.9 (0.5)	5.2 (0.3)	5.5 (0.3)	5.7 (0.4)	5.7 (0.9)	6.6 (1.6)
HbA1c Visit 5 (baseline)	4.7 (0.3)	5.4 (0.2)	5.9 (0.2)	6.8 (0.4)	6.0 (0.5)	8.0 (1.1)
Kidney function						
eGFR, ml/min/1.73 m^2	67.3 (19.2)	70.8 (15.2)	69.8 (17.0)	69.5 (17.2)	67.9 (18.5)	67.8 (19.6)
uACR, mg/g	29.6 (67.5)	20.1 (39.2)	21.0 (38.2)	32.5 (67.9)	31.7 (60.3)	49.6 (77.3)

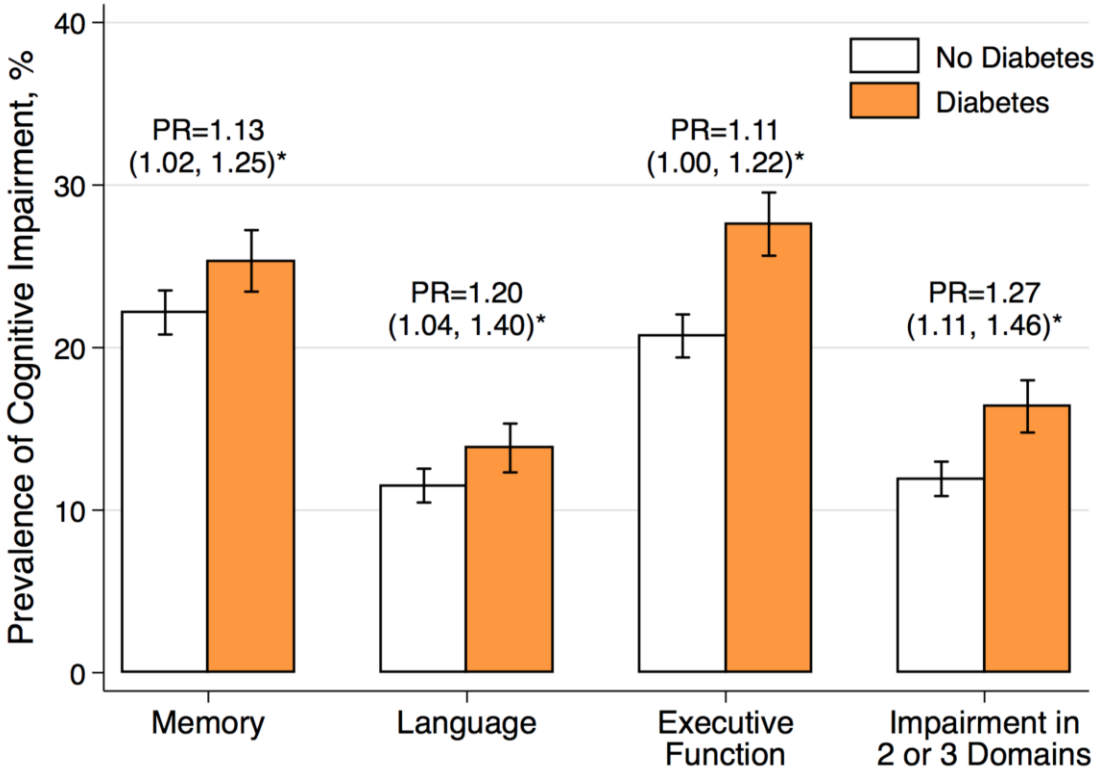
Values shown as mean (SD)

* Hypolipidemia was calculated as values below the 10th percentile in the entire population of visit 5 participants. Cutoffs were as follows: LDL-c <63.4 mg/dL; HDL-c <36 mg/dL; triglycerides <67 mg/dL; total cholesterol <131 mg/dL;

† HbA1c measurements obtained in 1990-1992, 21-23 years prior to the measurements in the present study

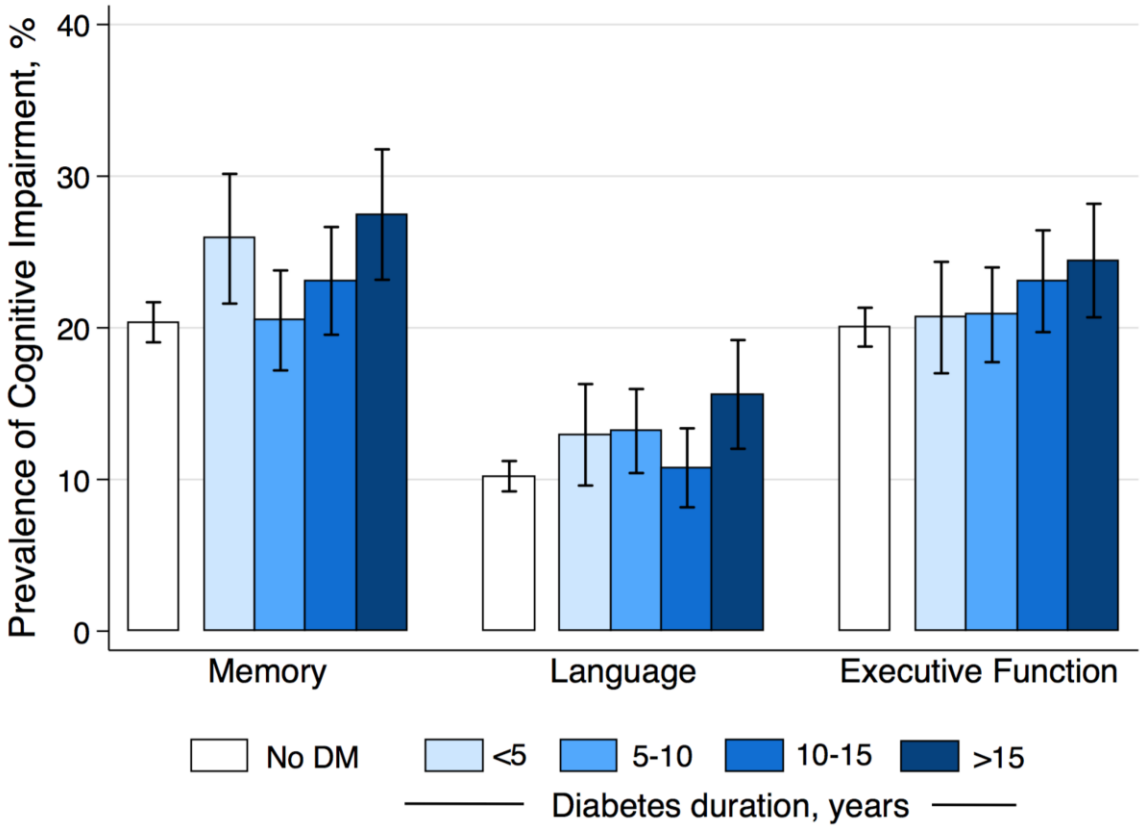
Abbreviations: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; uACR, urine albumin to creatinine ratio.

Supplemental Figure 1. Prevalence of cognitive dysfunction by diabetes status (diagnosed or undiagnosed diabetes, compared to persons with no diabetes and HbA1c <6.5%)



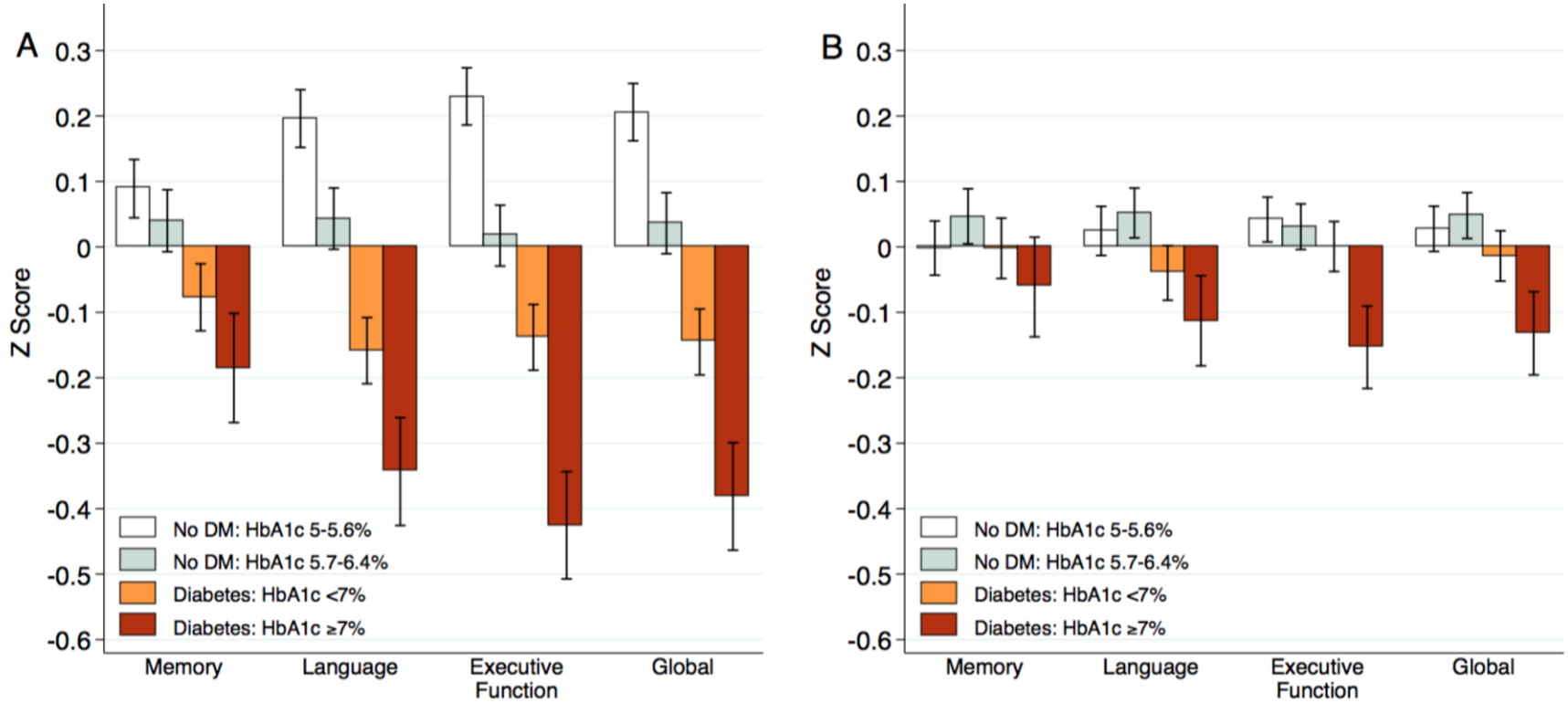
Legend: Prevalence estimates are shown unadjusted. Prevalence ratios (PRs) are from Poisson regression models adjusted for age, race, sex, education, hypertension, history of coronary heart disease, history of stroke, drinking status, cigarette smoking status, and APOE e4. Diabetes was defined based on self-reported physician diagnosis, diabetes medication use, or A1c ≥6.5%. Cognitive impairment in each domain was defined as test scores more than 1.5 standard deviations below age-, race-, and education-adjusted norms among 2 or more tests in a give domain.

Supplemental Figure 2. Adjusted prevalence of cognitive dysfunction by domain and diabetes duration



Legend: Prevalence estimates are from Poisson regression models adjusted for age, race, sex, education, hypertension, history of coronary heart disease, history of stroke, drinking status, cigarette smoking status, and APOE e4. Diabetes was defined based on self-reported physician diagnosis or diabetes medication use, and duration was calculated using the date a participant first reported a diagnosis or medication use (during a previous visit or during the annual follow-up telephone call). The group of participants without diabetes ("No DM") did not include participants with HbA1c ≥6.5%. Cognitive impairment in each domain was defined as test scores more than 1.5 standard deviations below age-, race-, and education-adjusted norms among 2 or more tests in a given domain.

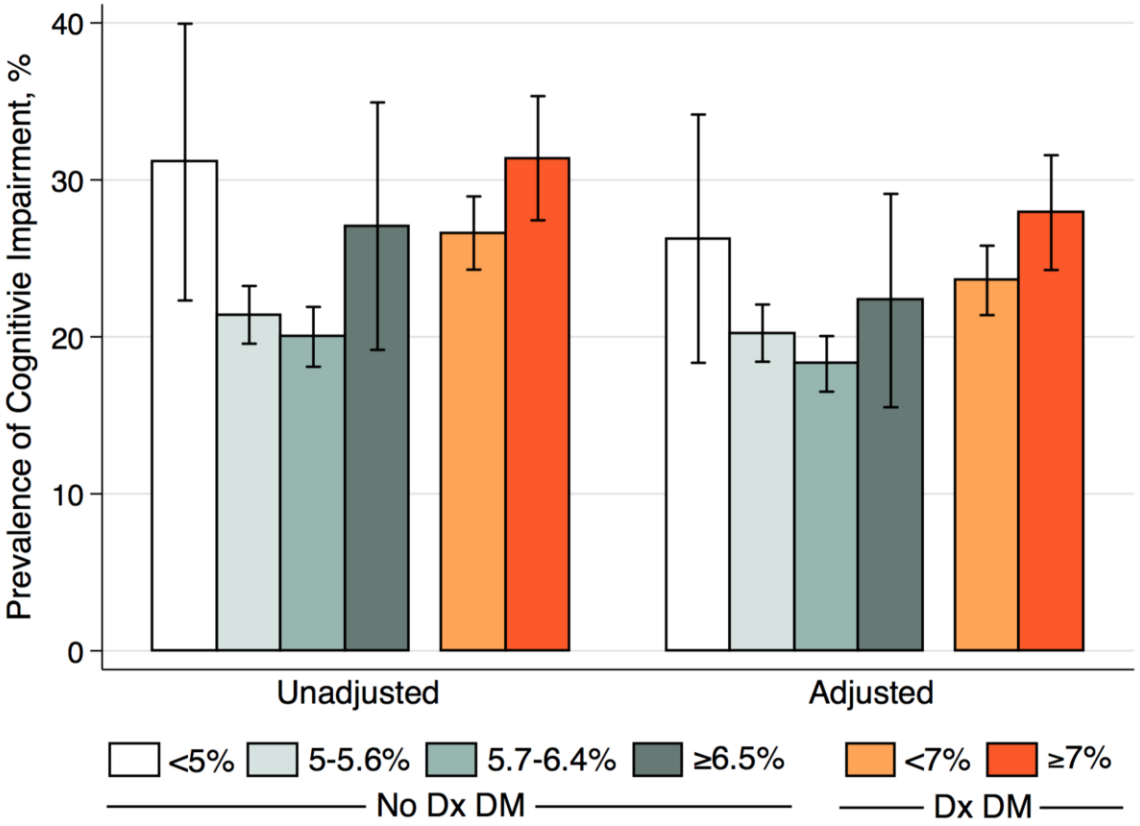
Supplemental Figure 3. Mean Global Z score by domain by no diabetes, prediabetes, and HbA1c control among persons with diabetes (diagnosed or undiagnosed diabetes, compared to persons with no diabetes and HbA1c <6.5%)



Diabetes ("DM") was defined based on self-reported physician diagnosis, diabetes medication use, or HbA1c ≥6.5%. Global Z score was calculated by taking the average of Z scores from eight neuropsychological tests, and was standardized to have a mean of 0 and a standard deviation of 1.

Panel A: unadjusted means
Panel B: means estimated from linear regression models with adjustment for age, race, sex, education, hypertension, history of coronary heart disease, history of stroke, drinking status, cigarette smoking status, and APOE e4.

Supplemental Figure 4. Prevalence of cognitive dysfunction defined by expert review of participants' medical information



Legend: Adjusted values are from a Poisson regression model with adjustment for age, race, sex, education, hypertension, history of coronary heart disease, history of stroke, drinking status, cigarette smoking status, and APOE e4. Diabetes was defined based on self-reported physician diagnosis or diabetes medication use. Cognitive impairment included algorithm diagnosis (included previous visit neurocognitive test scores (1990-1992 or 1996-1998), failure in domains at the current visit (2011-2013), scores from the clinical dementia rating) or review by committee (included neuropsychiatric information, medical/family history, participant or proxy report of memory complaints, neurological/physical examination/labs, imaging information from brain MRI at the 2011-2013 exam, and use of certain medications). MCI (N=1186) and dementia(N=160) were grouped to define cognitive impairment.

Curriculum Vitae

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PERSONAL DATA

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EDUCATION

Degrees

PhD	Epidemiology – Started August 2013 Johns Hopkins University, Baltimore MD Concentration: Cardiovascular Disease Epidemiology NIH/NHLBI Pre-doctoral Training Grant in Cardiovascular Disease Advisor: Elizabeth Selvin, PhD MPH
MS, 2011	Statistics Portland State University, Portland OR Advisor: Robert Fountain, PhD
BS, 2004	Economics and Social Science Portland State University, Portland OR

PROFESSIONAL EXPERIENCE

9/2013 -	Research Assistant (part-time), Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
9/2011 - 9/2013	Biostatistician, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
9/2009 - 9/2011	Mathematical Statistician (Supervisor), Demographic Statistical Methods Division, Redesign Statistical Methods Branch, U.S. Bureau of the Census
7/2006 - 9/2009	Mathematical Statistician, Demographic Statistical Methods Division, Victimization and Expenditures Branch, U.S. Bureau of the Census

PUBLICATIONS

1. Selvin, E, Halushka, MK, **Rawlings, AM,** Hoogeveen, RC, Ballantyne, CM, Coresh, J, & Astor, BC (2013). sRAGE and risk of diabetes, cardiovascular disease, and death. *Diabetes, 62*(6), 2116-2121. doi: 10.2337/db12-1528.
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2. Selvin, E, **Rawlings, AM**, Bergenstal, RM, Coresh, J, & Brancati, FL (2013). No racial differences in the association of glycated hemoglobin with kidney disease and cardiovascular outcomes. *Diabetes Care, 36*(10), 2995-3001. doi: 10.2337/dc12-2715.
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3. Foster, MC, **Rawlings, AM,** Marrett, E, Neff, D, Willis, K, Inker, LA, Selvin, E (2013). Cardiovascular risk factor burden, treatment, and control among adults with chronic kidney disease in the United States. *Am Heart J, 166*(1), 150-156. doi: 10.1016/j.ahj.2013.03.016.
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8. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, Coresh J, Knopman D, Power MC, **Rawlings A**, Sharrett AR, Wruck LM, Mosley TH. *Midlife Hypertension and 20-Year Cognitive Change: The Atherosclerosis Risk in Communities Neurocognitive Study*. JAMA Neurol. 2014 Aug 4. doi: 10.1001/jamaneurol.2014.1646.
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9. Selvin E, **Rawlings AM**, Grams M, Klein R, Steffes M, Coresh J. Association of 1,5-anhydroglucitol with diabetes and microvascular conditions. *Clin Chem.* 2014 Nov;60(11):1409-18. doi: 10.1373/clinchem.2014.229427. Epub 2014 Sep 8.
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Papers under review

Rawlings AM, Sang Y, Sharrett AR, Coresh J, Griswold M, Kucharska-Newton AM, Palta P, Wruck LM, Gross AL, Deal JA, Power MC, Bandeen-Roche K. Multiple Imputation of Cognitive Performance as an Outcome.

CONFERENCE PRESENTATIONS

Rawlings A, Castelo D. *Two Methods of Sampling New Construction for the Demographic Surveys Sample Redesign*. Joint Statistical Meetings American Statistical Association, Miami Beach, August 1, 2011.

Rawlings A, Sharrett AR, Schneider ALC, Coresh J, Albert M, Couper D, Griswold M, Gottesman R, Wagenknecht L, Windham GB, Selvin E. *Diabetes is a Risk Factor for 20-year Cognitive Decline*. AHA EPI/NPAM 2014, San Francisco, March 19, 2014.

CONFERENCE POSTERS

Bower JK, Nambi V, Lazo M, **Rawlings AM**, Foster MC, & Selvin E. *Glycated hemoglobin versus fasting glucose in defining metabolic syndrome and prediction of coronary heart disease*. American Heart Association Epidemiology & Prevention and Nutrition, Physical Activity & Metabolism 2013 Scientific Sessions, New Orleans, LA.

***Schneider AL, *Rawlings AM**, Sharrett AR, Alonso A, Mosley T, Hoogeveen R, Ballantyne CM, Gottesman RF, Selvin E. *Highly Sensitive Cardiac Troponin T is Associated with Cognitive Function and Incidence of Dementia.* American Heart Association Epidemiology & Prevention and Nutrition, Physical Activity & Metabolism 2013 Scientific Sessions, New Orleans, LA. ***Co-first authors.**

Selvin E, **Rawlings AM**, Bergenstal RM, Coresh J, Brancati FL (2013). *No Racial Differences In The Association Of Glycated Hemoglobin With Kidney Disease And Cardiovascular Outcomes.* American Heart Association Epidemiology & Prevention and Nutrition, Physical Activity & Metabolism 2013 Scientific Sessions, New Orleans, LA.

Rawlings AM; Sharrett AR; Knopman D; Parrinello CM; Palta P; Wruck L; Bandeen-Roche K; Gottesman RF; Albert M; Coresh J; Mosley T; Selvin E. *Prevalence of Cognitive Dysfunction Among Older Adults With Diabetes.* American Heart Association Epidemiology/Lifestyle 2015 Scientific Sessions, Baltimore, March 6, 2015

Rawlings AM; Sharrett AR; Maruthur NM; Parrinello CM; Rebholz CM; Steffes MW; Selvin E. *Glycemic Excursions and Cognitive Function in Older Adults With Diabetes.* American Heart Association Epidemiology/Lifestyle 2015 Scientific Sessions, Baltimore, March 6, 2015.

Upcoming posters

Rawlings AM; Sharrett AR; Mosley T; Ballew SH; Deal JA; Selvin E. *Glucose Peaks and Risk of Dementia among Persons with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study.* American Heart Association Epidemiology/Lifestyle 2016 Scientific Sessions, Phoenix, March 3, 2016.

Rawlings AM, Sang Y, Sharrett AR, Coresh J, Griswold M, Kucharska-Newton AM, Palta P, Wruck LM, Gross AL, Deal JA, Power MC, Bandeen-Roche K. *Multiple Imputation of Cognitive Performance as an Outcome: the Atherosclerosis Risk in Communities (ARIC) Study.* 2016 Epidemiology Congress of the Americas, Miami, June 22, 2016.

TEACHING

2015	Teaching Assistant, Stata Programming Johns Hopkins University (enrollment 200)
2015	Teaching Assistant, Assessment of Clinical Cardiovascular Disease Johns Hopkins University (enrollment 10)
2014	Lead Teaching Assistant, Epidemiologic Methods Johns Hopkins University (enrollment 265)

2013 Teaching Assistant, Epidemiologic Methods
Johns Hopkins University (enrollment 230)

AWARDS AND FELLOWSHIPS

2014 Jeremiah and Rose Stamler Research Award for New Investigators
(Award recognizes excellence in research, American Heart Association Epidemiology and Nutrition 2014)

2013 - NIH/NHLBI Pre-doctoral Training Grant in Cardiovascular Disease, Johns Hopkins University

2011 Department of Commerce Bronze Medal Award in Leadership, US Census Bureau
(Highest award presented by head of the Department of Commerce)

PROFESSIONAL DEVELOPMENT

2013 - American Heart Association Member

2015 - International Society to Advance Alzheimer's Research and Treatment

2015 - Society for Epidemiologic Research